DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

SEP 19 1997

Mr. Howard Holstein
Hogan and Hartson
Columbia Square
555 Thirteenth Street, N.W.
Washington, D.C. 20004

Re: P940016
H.E.L.P. (Heparin-induced Extracorporeal Lipoprotein Precipitation) System
Filed: June 1, 1994
Amended: August 16, 23, and December 2, 1994; January 10, March 24 (2), 28, 29 (2), 31, June 8, 15, July 28, August 11, September 1, 15, October 20, December 5, 8, and 22, 1995; February 8, 22, March 21, April 26, June 21 (2), 27, 28, July 18, August 13, September 16, October 24, November 8, 21, 27, December 6, and 19, 1996; January 7, 8, 21, March 6, April 4, August 14, September 5, 10, 11, and 12, 1997

Dear Mr. Holstein:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the H.E.L.P. System. The device is a low density lipoprotein cholesterol (LDL-C) apheresis system, indicated for use in performing LDL-C apheresis to acutely remove LDL-C from the plasma of the following high risk patient populations for whom diet has been ineffective and maximum drug therapy has either been ineffective or not tolerated: Group A - Functional Hypercholesterolemic Homozygotes with LDL-C > 500 mg/dl; Group B - Functional Hypercholesterolemic Heterozygotes with LDL-C ≥ 300 mg/dl; and Group C - Functional Hypercholesterolemic Heterozygotes with LDL-C ≥ 200 mg/dl and documented coronary heart disease (CHD).

Documented CHD is defined as having one or more of the following:

- a prior documented myocardial infarction (MI);
- a prior coronary artery bypass graft surgery (CABG);
- a prior percutaneous transluminal coronary angioplasty (PTCA) with or without atherectomy or coronary artery stent placement; and
- significant angina pectoris with a positive thallium or other heart scanning stress test.

Patients are eligible for H.E.L.P. therapy if, after a minimum of a 6-month trial of an American Heart Association (AHA) Step II diet (or equivalent) and maximum tolerated combination drug therapy designed to reduce LDL-C, they fall into Groups A, B, or C as defined above. In order to determine if a patient fits the LDL-C requirements of any of the groups (A, B, or C), baseline LDL-C levels need to be determined while patients are continuing on their diet

and drug therapies. A baseline LDL-C level is obtained by calculating the mean value of three serum samples obtained over a period of 2-4 weeks and collected after the patient has fasted overnight. All LDL-C values should be within 10 percent of each other, indicating a stable condition. If a patient's diet or drug therapy is modified, a new baseline LDL-C should be established. Maximum tolerated combination drug therapy is defined as an adequate trial of drugs from at least two separate classes of hypolipidemic agents such as, anion exchange resins/bile acid sequesterants, 3-hydroxy-3methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, fibric acid derivative, or niacin/nicotinic acid.

Although clinical benefit of LDL-C lowering has been documented in several diet, drug and/or surgical intervention trials, clinical studies using the H.E.L.P. System were not designed to address and did not establish the long-term clinical benefit of acutely lowering LDL-C.

We are pleased to inform you that the PMA is approved subject to the conditions described below and in the "Conditions of Approval" (enclosed). You may begin commercial distribution of the device upon receipt of this letter.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii), (1) insofar as the labeling specify the requirements that apply to the training of practitioners who may use the device as approved in this order and (2) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

In addition to the post-approval requirements in the enclosure, this approval is subject to a patient registry/post-approval study for all patients using the device. The patient registry/post-approval study will be conducted in two parts. The first part of the study encompasses the first 900 treatments with the device and is intended to gather additional safety and efficacy data of the following component modifications:

- precipitation filter;
- heparin adsorption filter;
- dialysis filter; and
- tubing set.

The second part of the study is open-ended and is a continuation of the post-approval study of safety and effectiveness of the device. Patient data for the entire (parts 1 and 2) study is to be collected and a report generated and submitted annually to FDA for review. This report will include a summary of

adverse events, morbidity and mortality statistics, analysis of lipid and chemistry laboratory results and summary statistics on demographics and other baseline characteristics of registry patients. In addition to the annual report, all patient deaths are to be reported to the FDA within 10 days after the applicant receives or has knowledge of information concerning a death. The mortality statistics are to be submitted on a quarterly basis and will include all patient information for patients who have died, whether the death is related or unrelated to the device. The timely reporting of such events is necessary owing to the limited device experience. The quarterly reports will continue until FDA determines this reporting frequency is no longer needed.

Expiration dating for this device has been established and approved at 5 years for the H.E.L.P. blood line set, 2 years for the H.E.L.P. Heparin Adsorber 500, 5 years for the H.E.L.P. Precipitate Filter, 18 months for the H.E.L.P. Plasmapheresis Filter, 2 years for the H.E.L.P. Ultrafilter. Expiration dating for the accessory solutions/concentrates which are compounded by B. Braun Melsingen have been established and approved at 3 years for the heparin sodium solution and the acidic bicarbonate hemodialysis concentrate, 1.5 years for the 0.9% sodium chloride solution and the sodium acetate buffer solution, and 1 year for the alkaline bicarbonate hemodialysis concentrate.

CDRH will publish a notice of its decision to approve your PMA in the FEDERAL REGISTER. The notice will state that a summary of the safety and effectiveness data upon which the approval is based is available to the public upon request. Within 30 days of publication of the notice of approval in the FEDERAL REGISTER, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the Federal Food, Drug, and Cosmetic Act (the act).

Failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

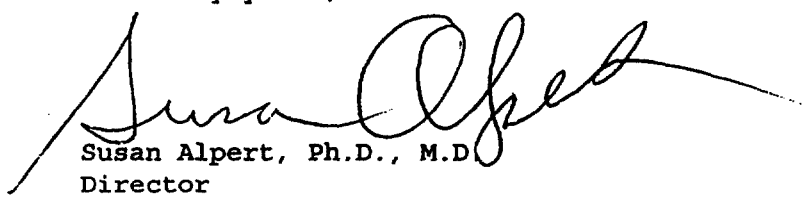
You are reminded that as soon as possible, and before commercial distribution of your device, that you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions concerning this approval order, please contact Ms. Linda Dart at (301) 594-1220.

Sincerely yours,



Susan Alpert, Ph.D., M.D.
Director
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

Issued: 5-2-95

CONDITIONS OF APPROVAL

APPROVED LABELING. As soon as possible, and before commercial distribution of your device, submit three copies of an amendment to this PMA submission with copies of all approved labeling in final printed form to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration (FDA), 9200 Corporate Blvd., Rockville, Maryland 20850.

ADVERTISEMENT. No advertisement or other descriptive printed material issued by the applicant or private label distributor with respect to this device shall recommend or imply that the device may be used for any use that is not included in the FDA approved labeling for the device. If the FDA approval order has restricted the sale, distribution and use of the device to prescription use in accordance with 21 CFR 801.109 and specified that this restriction is being imposed in accordance with the provisions of section 520(e) of the act under the authority of section 515(d)(1)(B)(ii) of the act, all advertisements and other descriptive printed material issued by the applicant or distributor with respect to the device shall include a brief statement of the intended uses of the device and relevant warnings, precautions, side effects and contraindications.

PREMARKET APPROVAL APPLICATION (PMA) SUPPLEMENT. Before making any change affecting the safety or effectiveness of the device, submit a PMA supplement for review and approval by FDA unless the change is of a type for which a "Special PMA Supplement-Changes Being Effected" is permitted under 21 CFR 814.39(d) or an alternate submission is permitted in accordance with 21 CFR 814.39(e). A PMA supplement or alternate submission shall comply with applicable requirements under 21 CFR 814.39 of the final rule for Premarket Approval of Medical Devices.

All situations which require a PMA supplement cannot be briefly summarized, please consult the PMA regulation for further guidance. The guidance provided below is only for several key instances.

A PMA supplement must be submitted when unanticipated adverse effects, increases in the incidence of anticipated adverse effects, or device failures necessitate a labeling, manufacturing, or device modification.

A PMA supplement must be submitted if the device is to be modified and the modified device should be subjected to animal or laboratory or clinical testing designed to determine if the modified device remains safe and effective.

A "Special PMA Supplement - Changes Being Effected" is limited to the labeling, quality control and manufacturing process changes specified under 21 CFR 814.39(d)(2). It allows for the addition of, but not the replacement of previously approved, quality control specifications and test methods. These changes may be implemented before FDA approval upon acknowledgment by FDA that the submission is being processed as a "Special PMA Supplement - Changes Being Effected." This acknowledgment is in addition to that issued by the PMA Document Mail Center for all PMA supplements submitted. This procedure is not applicable to changes in device design, composition, specifications, circuitry, software or energy source.

Alternate submissions permitted under 21 CFR 814.39(e) apply to changes that otherwise require approval of a PMA supplement before implementation of the change and include the use of a 30-day PMA supplement or annual postapproval report. FDA must have previously indicated in an advisory opinion to the affected industry or in correspondence with the applicant that the alternate submission is permitted for the change. Before such can occur, FDA and the PMA applicant(s) involved must agree upon any needed testing protocol, test results, reporting format, information to be reported, and the alternate submission to be used.

POSTAPPROVAL REPORTS. Continued approval of this PMA is contingent upon the submission of postapproval reports required under 21 CFR 814.84 at intervals of 1 year from the date of approval of the original PMA. Postapproval reports for supplements approved under the original PMA, if applicable, are to be included in the next and subsequent annual reports for the original PMA unless specified otherwise in the approval order for the PMA supplement. Two copies identified as "Annual Report" and bearing the applicable PMA reference number are to be submitted to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850. The postapproval report shall indicate the beginning and ending date of the period covered by the report and shall include the following information required by 21 CFR 814.84:

(1) Identification of changes described in 21 CFR 814.39(a) and changes required to be reported to FDA under 21 CFR 814.39(b).

(2) Bibliography and summary of the following information not previously submitted as part of the PMA and that is known to or reasonably should be known to the applicant:

(a) unpublished reports of data from any clinical investigations or nonclinical laboratory studies involving the device or related devices ("related" devices include devices which are the same or substantially similar to the applicant's device); and

(b) reports in the scientific literature concerning the device.

If, after reviewing the bibliography and summary, FDA concludes that agency review of one or more of the above reports is required, the applicant shall submit two copies of each identified report when so notified by FDA.

ADVERSE REACTION AND DEVICE DEFECT REPORTING. As provided by 21 CFR 814.82(a)(9), FDA has determined that in order to provide continued reasonable assurance of the safety and effectiveness of the device, the applicant shall submit 3 copies of a written report identified, as applicable, as an "Adverse Reaction Report" or "Device Defect Report" to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850 within 10 days after the applicant receives or has knowledge of information concerning:

(1) A mixup of the device or its labeling with another article.

(2) Any adverse reaction, side effect, injury, toxicity, or sensitivity reaction that is attributable to the device and

(a) has not been addressed by the device's labeling or

(b) has been addressed by the device's labeling, but is occurring with unexpected severity or frequency.

(3)Any significant chemical, physical or other change or deterioration in the device or any failure of the device to meet the specifications established in the approved PMA that could not cause or contribute to death or serious injury but are not correctable by adjustments or other maintenance procedures described in the approved labeling. The report shall include a discussion of the applicant's assessment of the change, deterioration or failure and any proposed or implemented corrective action by the applicant. When such events are correctable by adjustments or other maintenance procedures described in the approved labeling, all such events known to the applicant shall be included in the Annual Report described under "Postapproval Reports" above unless specified otherwise in the conditions of approval to this PMA. This postapproval report shall appropriately categorize these events and include the number of reported and otherwise known instances of each category during the reporting period. Additional information regarding the events discussed above shall be submitted by the applicant when determined by FDA to be necessary to provide continued reasonable assurance of the safety and effectiveness of the device for its intended use.

REPORTING UNDER THE MEDICAL DEVICE REPORTING (MDR) REGULATION. The Medical Device Reporting (MDR) Regulation became effective on December 13, 1984, and requires that all manufacturers and importers of medical devices, including in vitro diagnostic devices, report to FDA whenever they receive or otherwise became aware of information that reasonably suggests that one of its marketed devices

(1)may have caused or contributed to a death or serious injury or

(2)has malfunctioned and that the device or any other device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

The same events subject to reporting under the MDR Regulation may also be subject to the above "Adverse Reaction and Device Defect Reporting" requirements in the "Conditions of Approval" for this PMA. FDA has determined that such duplicative reporting is unnecessary. Whenever an event involving a device is subject to reporting under both the MDR Regulation and the "Conditions of Approval" for this PMA, you shall submit the appropriate reports required by the MDR Regulation and identified with the PMA reference number to the following office:

Division of Surveillance Systems (HFZ-531)
Center for Devices and Radiological Health
Food and Drug Administration
1350 Piccard Drive, 340
Rockville, Maryland 20850
Telephone (301) 594-2735

Events included in periodic reports to the PMA that have also been reported under the MDR Regulation must be so identified in the periodic report to the PMA to prevent duplicative entry into FDA information systems.

Copies of the MDR Regulation and an FDA publication entitled, "An Overview of the Medical Device Reporting Regulation," are available by written request to the address below or by telephoning 1-800-638-2041.

Division of Small Manufacturers Assistance (HFZ-220)
Center for Devices and Radiological Health
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

SUMMARY OF SAFETY AND EFFECTIVENESS DATA
THE H.E.L.P. SYSTEM

I. GENERAL INFORMATION

DEVICE GENERIC NAME: LDL APHERESIS SYSTEM

DEVICE TRADE NAME: THE H.E.L.P. SYSTEM

APPLICANT'S NAME AND ADDRESS:
B. BRAUN MEDICAL, INC.
824 TWELFTH AVENUE
PO BOX 4027
BETHLEHEM, PA 18018-0027

PREMARKET APPROVAL APPLICATION (PMA) NUMBER: P940016

DATE OF PANEL RECOMMENDATION: April 21, 1995

DATE OF NOTICE OF APPROVAL TO THE APPLICANT: SEP 19 1997

II. INDICATIONS FOR USE

The H.E.L.P. (Heparin-induced Extracorporeal Lipoprotein Precipitation) System is indicated for use in performing low density lipoprotein cholesterol (LDL-C) apheresis to acutely remove LDL-C from the plasma of the following high risk patient populations for whom diet has been ineffective and maximum drug therapy has either been ineffective or not tolerated:

Group A — Functional Hypercholesterolemic Homozygotes with LDL-C > 500 mg/dl;

Group B — Functional Hypercholesterolemic Heterozygotes with LDL-C ≥ 300 mg/dl; and

Group C — Functional Hypercholesterolemic Heterozygotes with LDL-C ≥ 200 mg/dl and documented coronary heart disease (CHD).

Documented CHD is defined as having one or more of the following:

- a prior documented myocardial infarction (MI);
- a prior coronary artery bypass graft surgery (CABG);
- a prior percutaneous transluminal coronary angioplasty (PTCA) with or without atherectomy or coronary artery stent placement ;
- significant angina pectoris with a positive thallium or other heart scanning stress test.

Patients are eligible for H.E.L.P. therapy if, after a minimum of a 6-month trial of both an American Heart Association (AHA) Step II diet (or equivalent) and maximum tolerated combination drug therapy designed to reduce LDL-C, they fall into Groups A, B, or C as defined above. In order to determine if a patient fits the LDL-C requirements of any of the groups (A, B, or C), baseline LDL-C levels need to be determined while patients are continuing on their diet and drug therapies. A baseline LDL-C level is obtained by calculating the mean value of three serum samples obtained over a period of 2-4 weeks and collected after the patient has fasted overnight. All LDL-C values should be within 10% of each other, indicating a stable condition. If a patient's diet or drug therapy is modified, a new baseline LDL-C level should be established. Maximum tolerated combination drug therapy is defined as an adequate trial of drugs from at least two separate classes of hypolipidemic agents such as anion exchange resins/bile acid sequesterants, 3-hydroxy-3methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, fibric acid derivative, or niacin/nicotinic acid.

Although clinical benefit of LDL-C lowering has been documented in several diet, drug and/or surgical intervention trials,[1-9] clinical studies using the H.E.L.P. System were not designed to address and did not establish the long-term clinical benefit of acutely lowering LDL-C.

III. DEVICE DESCRIPTION

Components

The H.E.L.P. System consists of three groups of components:

1. Plasmat®-secura
2. H.E.L.P. filter set
3. H.E.L.P. line set

The system must be connected to an AC power source and an external reverse osmosis (RO) water supply. In addition, 5 accessory solutions are required for each treatment.

1. The Plasmat®-secura consists of a mobile base frame, which is on wheels, and the following 4 separate compact modules that are placed on top of the base frame: dialysate, cascade, blood and communication. These modules encompass the reusable portion of the system, which contains the hardware (including seven pumps and various transducers) with electronics, and software. Through the aid of three interconnected microprocessors, the modules control the flow of blood from and back to the patient, in addition to controlling the patient's blood and plasma in the extracorporeal circuit. The modules also monitor blood and plasma parameters in the extracorporeal circuit, and monitor and control the extracorporeal solutions. Various functions are assigned to each microprocessor. The first microprocessor system, referred to as the function processor, controls and monitors the entire operation of the device. The second microprocessor system, called the control processor, monitors the function processor to ensure proper response to potentially hazardous events. The third microprocessor system, called the monitoring display processor, provides status information. A CRT display unit is connected to the Plasmat®-secura. All communications between the user and system are through this display and keys on its front panel. System parameters, such as temperatures, conductivities, pressures, flow rates, etc., are visually displayed and/or controlled via the display unit.

2. The H.E.L.P. extracorporeal filter set, consists of four filters through which the blood and plasma flow during treatment. Each filter in the series is a sterile disposable item intended for single use only. These four filters are:

   a. The H.E.L.P. Plasmapheresis Filter - A conventional 0.55 micrometer hollow fiber plasmapheresis filter (B. BRAUN MELSUNGEN AG HAEMOSELECT® 0.55 micrometer) with a polypropylene membrane used for blood/plasma separation.

   b. The H.E.L.P. Precipitate Filter - A special 0.45 micrometer filter (CORNING COSTAR QRII-M) utilizing a polycarbonate membrane designed to retain precipitate.

   c. The H.E.L.P. Heparin Adsorber 500 - A special filter using a diethylaminoethyl (DEAE) cellulose membrane to serve as an ion exchanger and heparin remover.

   d. The H.E.L.P. Ultrafilter - A conventional hollow fiber dialyzer (TORAY FILTRYZER BI-1.3H) with a polymethylmethacrylate membrane used for bicarbonate hemodialysis. This filter is intrinsically connected to a complete hemodialysis system (Dialysate Compact Module) contained on the mobile cart.

3. The H.E.L.P. blood-line set is comprised of nine polyvinyl chloride (PVC) blood lines with air catchers and transducer protectors.

   These lines serve as interconnectors between the patient, filters, and pumps. The precipitate chamber in the circulation line is the chamber in which the complexing reaction occurs. All lines are sterile and disposable, and are intended for single use only.

Accessory Solutions

The following 5 solutions are used in the H.E.L.P. System treatment:

1. 0.9% Sodium chloride solution

   This solution is used for rinsing and priming the assembled lines and filters prior to treatment. Approximately 6 liters (L) of sodium chloride solution is used to flush tubing and extracorporeal components and approximately 5 L of solution is used for the actual treatment. This solution is compounded by B. Braun Melsingen (BBM) in Germany. It is provided sterile at a pH between 4.5 and 7.0.

2. 0.3M Sodium Acetate buffer solution

   This solution is mixed with the patient's plasma and adjusts the pH of the plasma to the optimal pH (5.12) for LDL-C and heparin to form a complex. The system requires 3 L of sodium acetate buffer per procedure. This solution is compounded by BBM in Germany and is provided sterile at a pH between 4.75.and 4.95.

3. Heparin sodium solution:

   This solution is used to complex with and precipitate out LDL-C. It is injected into the sodium acetate buffered plasma (pH 5.12) and forms a complex with LDL-C which then precipitates out of solution. Thirty milliliters (ml) (300,000 International Units (IU) heparin) of this solution is used per procedure. This solution is compounded by BBM in Germany. It is provided sterile at a pH between 5.5 to 8.0.

4. Acidic bicarbonate hemodialysis solution (from concentrate):

   This powdered concentrate is compounded by BBM and mixed with in-house RO water by the device. This solution is used, together with alkaline bicarbonate hemodialysis solution, to provide bicarbonate hemodialysis in order to remove acetate from the treated plasma and to restore the plasma to physiological pH for re-infusion to the patient. The H.E.L.P. System uses 6 L of acidic bicarbonate hemodialysis solution for each procedure. The concentrate is not provided sterile.

5. Alkaline bicarbonate hemodialysis solution (from concentrate):

   This concentrate is compounded by BBM and mixed with in-house RO water by the device. This solution is used, together with acidic bicarbonate hemodialysis solution, to provide bicarbonate hemodialysis in order to remove acetate from the treated plasma and to restore the plasma to physiological pH for re-infusion to the patient. The H.E.L.P. System uses 10 L of alkaline bicarbonate hemodialysis solution for each procedure. The concentrate is not provided sterile.

A description of how the solutions are connected to the H.E.L.P. System disposables is available in the operator's manual.

Principle of Operation

H.E.L.P. therapy is a treatment for lowering total blood cholesterol as well as LDL-C levels by direct removal from the bloodstream.[1-5] The procedure requires venous (vein to vein, arteriovenous (A-V) fistula, or central venous (CV)) access. As blood is removed, plasma and red blood cells are separated by a 0.55 micrometer hollow-fiber filter. The plasma is then mixed in the precipitate chamber with a sodium acetate buffer (pH 4.85) containing 100 units per ml of heparin to achieve a final plasma pH of 5.12. At this pH, LDL-C and heparin form a complex which precipitates out of solution. The plasma then passes through a 0.45 micrometer polycarbonate filter which filters out the LDL-C/heparin complex. The plasma is then filtered through a DEAE cellulose filter where excess heparin is adsorbed. Finally, the plasma is passed through the ultrafilter where the pH is restored through bicarbonate dialysis and excess fluid is removed before the treated plasma is mixed with the blood cells which had been removed earlier, and both are returned to the patient. The entire procedure takes about 1.5 hours. This new treatment is to be used only in patients who meet the conditions for Group A, B or C (described above), after being stabilized on optimal diet and drug therapy.[5-9]

IV. CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS

LDL apheresis with the H.E.L.P. System is contraindicated in patients:

1. for whom the use of heparin would cause excessive or uncontrolled anticoagulation or for whom adequate anticoagulation cannot be safely achieved, such as patients with hemophilia or patients who have had recent surgery; or

2. with known hypersensitivity to heparin or ethylene oxide.

The warnings and precautions can be found in the H.E.L.P. System labeling.

V. ALTERNATIVE PRACTICES OR PROCEDURES

Diet and drug therapy, either alone or in combination, are initially used for reducing cholesterol levels and are adequate in most individuals. For those with more severe forms of hypercholesterolemia (HC), more aggressive measures may be required. These have included plasmapheresis, other extracorporeal LDL-C removal devices and surgical interventions such as ileal bypass, portacaval shunt, and liver transplantation.

VI. MARKETING HISTORY

The H.E.L.P. System is currently marketed in Germany and Italy. The H.E.L.P. System has not been withdrawn from marketing in any jurisdiction for any reason relating to the safety and effectiveness of the device.

VII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE

Potential adverse reactions associated with LDL-apheresis using the H.E.L.P. System are those which have been observed in other procedures involving extracorporeal circulation. Potential adverse events include those adverse events that occurred during the clinical studies, as well as other adverse effects potentially associated with this type of treatment.

As indicated in Tables 10 and 11, the following adverse events were reported in the U.S. clinical study (2,826 treatments) and/or the German clinical study (21,305 treatments): venous access problems; hypotension; fatigue; chills and shivering; prolonged partial thromboplastin time or activated clotting time (includes reports on patients whose blood samples were drawn through heparinized cardiovascular lines); nausea and vomiting; chest heavy/pain; dizziness/syncope; ache; elevated temperature; gastrointestinal (GI) bleed; flushing; hyperventilation; wheezing; elevation of liver enzymes; apical density of CXR; ankle swelling; prostatitis; hematuria; hypoglycemia; sympathetic reflex dystrophy; angina/2nd PTCA; endarterectomy; myocardial infarction (MI)/death, bradycardia; tachycardia; vertigo; collapse; hypertension; angina pectoris; hematoma; shunt occlusion; hemolysis; other rhythm problems; prolonged bleeding time; edema; headache; sweating; fever; eyes burning; arrhythmia; systemic allergic reaction; swelling of face and hands; disturbed cutaneous sensitiveness; muscle, bone, and joint pain; restlessness; dyspnea; cough; bleeding; GI complaints; dysphagia; polyuria; and insomnia.

Other adverse effects potentially associated with this type of treatment include systemic reactions resulting from decreased blood volume during treatment, changes in blood temperature following the treatment, introduction of foreign compounds into the bloodstream, infection at the incision site, and potential heart failure. Other possible concerns include the following: air embolism associated with the extracorporeal circuit;

steal-syndrome, a known risk to A-V fistulas; the risk of the A-V fistula clotting in a non-uremic state; bleeding secondary to inadequate de-heparinization or reduced fibrinogen levels; inadequate removal of acetate; depression of cardiac function as a result of the use of citrates; idiosyncratic reaction to system materials; problems resulting from failure to restore physiologic pH; unknown potential interactions with other compounds present in the bloodstream; and unknown potential selective adsorption of other compounds present in the bloodstream.

Although LDL-apheresis is very selective in removing LDL-C, other plasma components are also removed. These plasma components include high density lipoprotein cholesterol (HDL-C), fibrinogen, plasma proteins, platelets and ferritin. The long-term effects of this is not known. In the U.S. clinical study, mean reductions in these plasma components were as follows: HDL-C, -13.6%; fibrinogen, -58.0%; apolipoprotein A-1, -16.8%; apolipoprotein B, -55.4%; platelets, -10.1%; and ferritin, -16.0%.

Patients on certain antihypertensive drugs may have an increased risk of hypotension during extracorporeal treatment. To minimize the risks associated with the concomitant use of antihypertensive drugs, patients should refrain, if the patient's physician agrees, from taking the medication on the day of the H.E.L.P. System treatment until after the treatment is completed.

Patients who are on concurrent drug therapy also face the risks attendant to the drug being taken. Since most drugs are transported bound to albumin and the H.E.L.P. System could remove albumin, reduced drug levels could be expected immediately after treatment.

There were no adverse events due to device failure.

See the Section IX, Summary of Clinical Studies, for additional information on adverse events.

VIII. SUMMARY OF PRECLINICAL STUDIES

Biocompatibility Testing

The biocompatibility of materials in the H.E.L.P. System filters and blood lines, either in direct or indirect contact with blood, was established through the use of materials in legally marketed medical devices with the same general intended use and/or by conducting biocompatibility testing on component materials and on the finished, sterilized device. Testing of the finished, sterilized device was carried out using the heparinized first saline flush through the H.E.L.P. System. Cytotoxicity, sensitization, skin irritation, intracutaneous reactivity, systemic toxicity, sub-chronic toxicity, mutagenicity, hemolysis, and pyrogenicity were assessed. The results demonstrated that the finished, sterilized device was safe for its intended use.

Bench Testing

Bench testing was conducted to assess various aspects of heparin induced precipitation of lipoproteins, including the relative ease of precipitating lower density lipoproteins compared to higher density lipoproteins, the effect of heparin molecular weight on LDL-C precipitation, the effect of pH and heparin concentration on precipitation of LDL-C and total plasma proteins, the concentration of heparin required to precipitate LDL-C from serum compared to precipitation of LDL-C from plasma, the composition of precipitated lipoproteins as a function of pH, and the precipitation of individual plasma proteins as a function of pH.

Experiments were conducted to optimize the standard precipitate filter cartridge in order to overcome challenges presented by patients with elevated fibrinogen levels or extreme blood viscosity. The efficiency of the optimized filter configuration was demonstrated by *in vitro* studies in which human fresh frozen plasma heated to 37° C was treated and hydrostatic pressure was monitored on the retention and on the filtration side of the filter arrangement.

The specificity of the precipitate filter configuration was demonstrated by treating plasma and analyzing the treated plasma that was captured after the ultrafiltration filter. The LDL-C was found to have been significantly reduced, while HDL-C was only insignificantly reduced as were protein and albumin. Another study looked at adsorptive binding of plasma proteins to the filter membrane and demonstrated that none of the plasma proteins studied were adsorbed to the precipitate filter in a significant quantity.

The heparin adsorber was designed to have a high heparin and low protein binding capacity. Testing was conducted to demonstrate the binding capacity of the heparin adsorber under simulated use conditions in which larger amounts of heparin were used than would be used during treatment with the H.E.L.P. System. The results showed that the heparin adsorber is capable of binding much larger amounts of heparin than are necessary during treatments with the H.E.L.P. System. In addition, DEAE binding profiles were generated to establish that the function of the heparin adsorber is not affected by acid buffer solution. Stability testing on the heparin adsorber has also been conducted and includes the following tests: housing integrity, pressure drop, DEAE adsorption capacity, particle count after rinses, sterility, pyrogens, bacterial endotoxins, and, after rinses, concentrations of hemolytic substances, total nitrogen, total organic carbon, acetate, non acetate carbon, and oligomeric/polymeric substances.

Testing was carried out on the ultrafiltration filter using fresh frozen plasma under conditions simulating clinical treatment, with the exception that the plasma was not conveyed through the plasmapheresis filter. Samples of plasma were collected at the ultrafilter inlet and outlet and tested for acetate concentration. The pH was measured

at the outlet. The results demonstrated that the filter effectively reduces the plasma/buffer acetate concentration and restores physiological plasma pH.

Shelf Life Testing

The applicant provided a protocol and the results of limited testing to establish the minimum shelf life for the disposable components of the H.E.L.P. System. These disposable components include, the blood line set, the heparin adsorber, the precipitate filter, the plasma filter, and the Ultrafilter.

The following tests established a shelf life of 5 years for the blood line set: product integrity, package integrity, biological (sterility, hemolysis, and pyrogenicity), and chemical (reducing substances, residue of evaporation, buffering capacity, UV absorbance, and heavy metal content).

The following tests established a shelf life of 2 years for the heparin adsorber: product integrity (housing integrity, air flow, and pressure drop), package integrity, adsorption capacity, microparticle leakage, biological (sterility, hemolysis, and pyrogenicity), and chemical (nitrogen, organic carbon, acetate, non-acetate carbon, oligomeric/polymeric substances).

The following tests established a shelf life of 5 years for the precipitate filter: product integrity (visual check, pressure test), package integrity, chemical (appearance, reducing substances, buffering capacity, heavy metals, evaporation residue, ammonium, and absorbance), microparticle leakage, and biological (sterility, hemolysis, and pyrogenicity).

The following tests established a shelf life of 1.5 years (18 months) for the plasma filter: product integrity (visual check), package integrity, chemical (reducing substances, residue of evaporation, buffering capacity, UV absorbance, and heavy metal content), microparticle leakage, and biological (sterility, hemolysis, and pyrogen).

The following tests established a shelf life of 2 years for the Ultrafilter: product integrity (visual check, pressure test), package integrity, chemical (acidity/alkalinity, reducing substances, residue on evaporation, heavy metals, absorbance), and biological (sterility and hemolysis).

The following tests established a shelf life of 1.5 years (18 months) for the 0.9% sodium chloride and sodium acetate buffer solutions: pH and chemical analysis, particulate count, sterility and pyrogenicity testing.

The following tests established a shelf life of 3 years for the heparin sodium solution: pH and chemical analysis, particulate count, sterility and pyrogenicity testing.

The following tests established a shelf life of 3 years for the acidic bicarbonate hemodialysis concentrate: appearance and chemical and pH analysis.

The following tests established a shelf life of 1 year for the alkaline bicarbonate hemodialysis concentrate: appearance and chemical and pH analysis.

Software Testing

Testing of the software included both module testing and functional system testing. Testing was conducted as part of the software development process. This included the validation testing and the testing of hazard conditions on the finished device.

Software Validation validated system accuracy, operation, and performance. Normal and abnormal processing modes were validated including data entry, displays, control sequences, range limits, alarms, and error conditions. Module level testing validated that each module performed as designed. The complete system was validated under normal operating conditions, using the Operator's Manual to ensure correct operation.

The results of the software testing showed that the software did perform according to specifications and that the design was appropriate for its intended use.

Electrical Safety Testing

The device was tested and shown to meet IEC standard 601-2-16 (1993), "Medical Electrical Equipment -- Part I: General Requirements for Safety. Part II: Collateral Standard: Electromagnetic Compatibility -- Requirements and Tests."

IX. SUMMARY OF CLINICAL STUDIES

Objectives

Objectives of the U.S. study were to evaluate the safety and effectiveness of the H.E.L.P. System in hypercholesterolemic patients with plasma LDL-C concentrations above 160 mg/dl while on appropriate diet and drug therapy for at least 12 weeks.

Safety evaluations were based on adverse effects and laboratory endpoints.

Effectiveness evaluations were based on changes in plasma LDL-C and total cholesterol (TC) levels, both before and after individual treatments across the course of weekly or biweekly treatments.

The objectives of the study conducted in Germany were to evaluate the safety and efficacy of the H.E.L.P. System in hypercholesterolemic patients with coronary artery disease who had:

- plasma LDL-C concentration above 200 mg/dl despite diet and drug therapy, and
- clinically apparent coronary artery disease with angiographically proven changes in more than one segment of the coronary artery tree.

Safety evaluations were based on adverse effects and laboratory endpoints. Effectiveness evaluations were based on a comparison of findings before and after H.E.L.P. therapy. Angiographic studies were conducted at baseline to demonstrate CHD and, after 2 years, to assess the CHD status of patients who have received weekly H.E.L.P. therapy.

Study Design

The U.S. study and the German study were both multi-center clinical trials of the H.E.L.P. System. The U.S. study was conducted under an Investigational Device Exemption Application (IDE G880286) at four centers. One of these U.S. centers continues to treat six patients under the IDE.

The German BMFT Study was conducted at nine centers in Germany and Italy using the same protocol and the same device. Neither the U.S. or the German study included control groups.

U.S. Study:

Patients were enrolled in the U.S. study if they met the following criteria:

Inclusion Criteria

1. Age: not less than 25 or older than 70 years except for functionally homozygous familial hypercholesterolemia patients, who could have been 7 years of age or older.

2. Gender: males and post-menopausal, bilateral oophorectomized, or functionally homozygous familial hypercholesterolemic females.

3. Plasma or serum LDL-C concentration > 160 mg/dl despite a minimum of 12 weeks of Step 1 (National Cholesterol Education Program (NCEP) Guidelines) dietary therapy and drug therapy appropriate for their hypercholesterolemia.

4. Stable heart disease whether symptomatic or asymptomatic. Coronary atherosclerosis could be present, with or without angiographic evidence.

5. Laboratory values: hematocrit 30% or greater; platelet count between 100,000 and 1,000,000 platelets/ml.

6. Informed consent prior to baseline evaluation for study treatment, with the consent form signed by the patient or the patient's legally authorized representative.

Exclusion Criteria

1. Presence of any of the following conditions: hypothyroidism; congestive heart failure or major arrhythmia; renal insufficiency (creatinine greater than 2.0 mg/dl); uncontrolled diabetes mellitus; malignancy; disorders associated with excessive bleeding (e.g., peptic ulcer and hemophilia); established or suspected intracranial disease which might cause intracranial bleeding if patient is anticoagulated; or any other medical disorders which the Investigator and the Medical Monitor agreed would make study participation not be in the best interest of the patient.

2. Body weight 1.5 times greater than ideal as defined by 1983 Metropolitan Life Insurance Company Weight Tables.

3. Fasting triglycerides >500 mg/dl.

4. Diastolic blood pressure (BP) > 100 mm Hg recorded on two occasions at least 24 hours apart.

5. Positive tests for acute Hepatitis (A or B) or human immunodeficiency virus (HIV) or diagnosis of acquired immunodeficiency syndrome (AIDS).

6. Current treatment with anticoagulants or with any investigational product.

7. Immunosuppressed patient.

Patients were continued on pre-study diet and drug regimens so that no major changes in plasma cholesterol levels would occur due to changes in diet and drug therapy.

German Study:

Patients were enrolled in the German study if they met the following criteria:

Inclusion Criteria

1. Age: under 65 years of age.
2. Gender: males and females.
3. Hypercholesterolemia with an LDL-C level greater than 200 mg/dl despite diet and drug therapy.
4. Clinically apparent coronary artery disease with angiographically proven significant stenosis in one or more segments of the coronary artery tree.
5. Consent of the patient to undergo long-term extracorporeal H.E.L.P. therapy and repeat angiography.

Exclusion Criteria

1. Coagulopathy, hemorrhagic diathesis, neoplasms, liver disease, severe forms of congestive heart failure, valvular cardiac disease, cerebral vascular accidents, or dementia.
2. Unwillingness to adhere to medically advised drug and diet regimens.
3. Participation in another investigational therapy study.

The patients who received treatments in clinical trials of LDL-apheresis devices (both U.S. and German studies) were classified into three groups that were defined as follows:

- Group A: functional hypercholesterolemic homozygotes, defined as patients whose LDL-C levels were >500 mg/dl after 6 months of diet and drug therapy,
- Group B: severely-affected functional hypercholesterolemic heterozygotes, defined as patients whose LDL-C levels were 300-500 mg/dl after 6 months of diet and drug therapy, and
- Group C: functional hypercholesterolemic heterozygotes, defined as patients with LDL-C levels 200-299 mg/dl after 6 months of diet and drug therapy and with coronary heart disease.

The following presents the number of patients/treatments in the two studies who met these definitions:

	Patients	Treatments
Group A	4	400
Group B	32	2405
Group C	30	2365
Other	25	1249
Total	91	6419

Effectiveness data on the 66 patients in the three subgroups (A, B and C) were presented in the PMA and used to assess the effectiveness of the H.E.L.P. System in the three target patient groups. However, the clinical protocol of the U.S. study allowed the enrollment of patients with LDL-C levels of 160 - 199 mg/dl. Thus, an additional 25 patients were treated who did not fit into one of the retrospectively defined categories noted above. Safety data from all treatments for all 91 treated patients were analyzed and presented in the PMA. Of the total of 91 patients treated, 77 were treated for at least 6 months and 66 for at least 1 year.

Mean age in the 91 treated patients was 45.2 years; the mean age was similar in all three subgroups. The youngest patient treated was 15 years old and was enrolled in the German study. Most of the treated patients were Caucasian.

Table 1
Patient demographics

Demographics	Group A	Group B	Group C
Age (in years):			
Mean	**38.8**	**42.3**	**47.7**
Range	**28-45**	**15-66**	**32-65**
Race:			
Caucasian	**100.0%**	**96.9%**	**100.0%**
Black	**0.0%**	**0.0%**	**0.0%**
Other	**0.0%**	**3.1%**	**0.0%**

Overall, there were 60 males and 31 females. In the three subgroups (A, B and C), there were 40 males and 26 females. There did not appear to be any selection bias on the basis of gender. At the ages represented in these studies (mean age for all groups is less than 47 years) women tend to be at less risk of CHD due to the benefits of the female hormone, estrogen. Therefore, except for Group A, the higher percentage of males in this study reflects that found in the general population for CHD.

Treatment Protocol

In the U.S. study, patients were evaluated according to the following schedule: screening (to determine eligibility), baseline (to determine patient status pre-treatment), H.E.L.P. treatment evaluations, 6 month and annual evaluations, and post-study evaluation.

An extensive screening evaluation was done on each patient prior to study enrollment to assure that eligibility criteria were met and informed consent was obtained. The medical history included type and duration of lipid-lowering drug therapy, type and duration of diet therapy, and antihypertensive drug therapy. Evaluation for heart disease, hypothyroidism, renal insufficiency, malignancy, uncontrolled diabetes mellitus, immunosuppression, and disorders associated with excessive bleeding or intracranial disease which might cause intracranial bleeding was done. Laboratory tests included routine CBC (hemoglobin, hematocrit, WBC count, WBC differential, platelet count), lipids (total cholesterol, total triglycerides, high density lipoprotein cholesterol (HDL-C), and calculated LDL-C), coagulation studies, as well as HIV and hepatitis A and B screening.

Patients were initiated onto a schedule of weekly treatments for a period of 6 months (25 treatments). After completion of 25 treatments, the patients were switched to biweekly treatments for the second 6 months of the protocol (through Treatment 37). After the second 6 months of therapy, patients were continued on the schedule that afforded the patients the most effective control of their hypercholesterolemia in the judgment of the treating physician (i.e., either weekly or biweekly) with a preference for biweekly therapy for up to 24 months. A select group of patients was continued in treatment for up to 60 months, following a weekly or biweekly regimen as appropriate at the discretion of the principal investigator.

In the German study, patients were treated weekly for the 24 month duration of the study period and were evaluated according to the following schedule: at screening (to determine eligibility), before and after each H.E.L.P. treatment, and at 6 month intervals during the course of the 24 month study period.

In both studies, each treatment had a target of treating one plasma volume (3000 ml).

Clinical Endpoints

Effectiveness of the H.E.L.P. System was based on changes in plasma LDL-C and total cholesterol (TC) levels, both before and after individual treatments across the course of weekly or biweekly treatments

Clinical Results

1. Acute Lipid Reduction

Table 2 presents the mean acute reduction of LDL-C, TC, and high density lipoprotein cholesterol (HDL-C) with each H.E.L.P. treatment for each of the three subgroups.

Table 2

Mean and Range of Acute Percent Change: Across Each Treatment*

Patient Subgroup	Number of Patients	LDL-C Mean Change (mg/dL)	LDL-C Change (%)	TC Mean Change (mg/dL)	TC Change (%)	HDL-C Mean Change (mg/dL)	HDL-C Change (%)
Group A	4	-200.7 (-487 to -77)	-63.6 (-78.1 to -24.5)	-218.1 (-515 to -85)	-57.3 (-701 to -24.5)	-7.7 (-25 to 6)	-17.1 (-46.1 to 24.0)
Group B	32	-147.7 (-416 to -15)	-62.0 (-95.2 to -5.0)	-162.0 (-433 to -14)	-51.9 (-76.2 to -4.1)	-5.8 (-102 to 67)	-12.8 (-75.9 to 231.0)
Group C	30	-116.9 (-260 to -14)	-59.8 (-91.4 to -8.8)	-133.7 (-267 to -3)	-48.9 (-77.7 to -2.0)	-6.6 (-95 to 65)	-13.7 (-89.2 to 382.4)

- Ranges are provided in parentheses.

As can be seen, average reductions in LDL-C well in excess of 50% occurred with each treatment. Conversely, the average reductions in HDL-C levels were 12% to 17% for each treatment. Although this demonstrates the relative selectivity of the procedure for LDL-C, epidemiological studies have shown that both low levels of HDL-C and high levels of LDL-C are independent risk factors for coronary heart disease and the risk of acutely lowering HDL-C levels while lowering LDL-C levels is unknown.

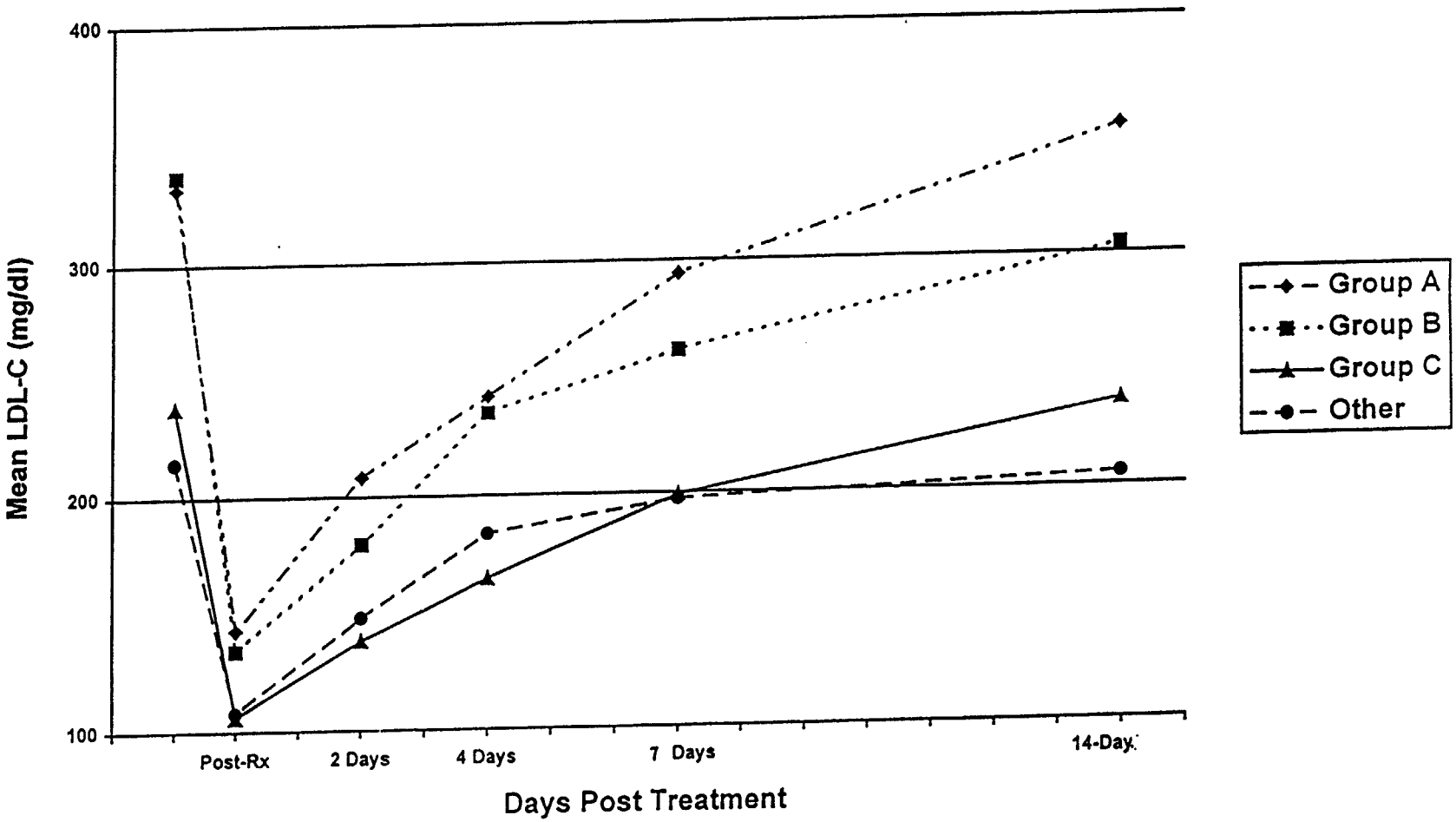
It should be noted that the distribution of HDL-C values post-H.E.L.P. therapy seen in Table 2, suggesting that some patients have a substantial increase in their HDL-C levels, is misleading. Heparin administration is known to produce, transiently, lipoproteins which may fall into the HDL category, but are not true HDL-C. Many patients who have hypertriglyceridemia at the beginning of therapy have an increase in these lipoproteins which are incorrectly measured as HDL-C These proteins disappear gradually after heparin in the plasma is metabolized. This effect occurs *in vivo* and even in the test tube after the blood is drawn. This phenomenon has been known for decades and is considered harmless to the patient. [10-15]

2. LDL-C POST-TREATMENT KINETICS ANALYSIS

In the U.S. study, LDL-C kinetic studies were performed on a limited number of patients after they had been switched from weekly treatment to biweekly treatment. Thirteen patients were studied during 21 treatments, with samples taken before and after treatment, at 24 hours, 48 hours, 96 hours, 7 days and 14 days post-treatment. The 21 treatments consisted of three treatments for the one patient in Group A, two treatments for the one patient in Group B, a total of three treatments for the two patients in Group C, and a total of 13 treatments for the nine patients in the "other" category. The results are shown in Figure 1.

FIGURE 1

Mean LDL-C Rebound



As shown in the figure, treatment with the H.E.L.P. System produces an immediate, rapid fall in LDL-C levels. However, LDL-C levels begin to increase following each treatment, with the most rapid rate of increase occurring in the first 4 days. LDL-C levels return to 50% of baseline in a mean time of 4.67 days.

Table 3 provides the range of rebound of LDL-C after treatment during the study period.

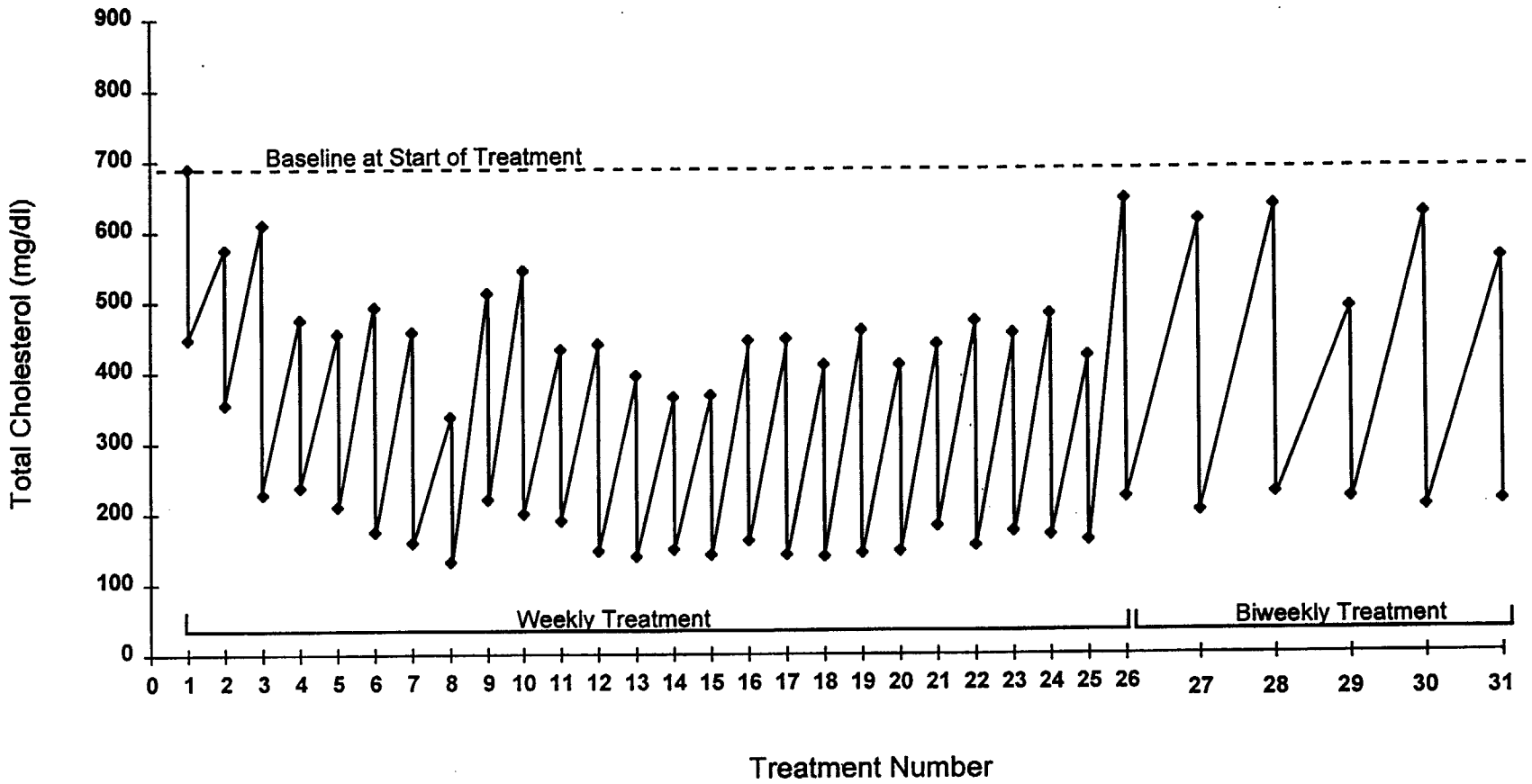
Table 3
Range of rebound of LDL-C after treatment during study period

Number of Days After Treatment	Cumulative Mean Percentage Rebound to Baseline			
	Group A (1 patient, 3 treatments)	Group B (1 patient, 2 treatments)	Group C (2 patients, 3 treatments)	Other * (9 patients, 13 treatments)
2	62 - 64	51 - 55	46 - 64	50 - 104
4	68 - 80	60 - 81	56 - 80	74 - 136
7	81 - 100	71 - 86	68 - 95	81 - 140
14	94 - 123	73 - 110	94 - 102	84 - 116

* One patient studied in the kinetics sub-study had an LDL-C level of 124 mg/dl prior to treatment. That patient's levels rose to 174 mg/dl during the follow-up period which represents 140% of the baseline level. When that patient was removed from the analysis the upper value of the ranges decreases substantially at each day: 24% on day 2, 93% on day 4, and 104% on day 7.

Without regular treatments, a patient's LDL-C and TC levels will rebound to the baseline level achieved with diet and drug therapy. The rate of rebound will accelerate if diet and lipid lowering are discontinued. With regular weekly H.E.L.P treatments, a patient's cholesterol levels can be maintained below the baseline level. As shown in Figure 2, TC levels were maintained at a lower level when the patient received weekly treatments than when biweekly treatments were given.

Total Cholesterol Levels in a Homozygote Patient Receiving H.E.L.P. Therapy



3. Coronary Angiography Results

There were 33 patients who completed 2 years of weekly H.E.L.P. therapy and had both baseline and 2 year coronary angiographies. These patients had a mean age of 47.2 years; 23 were males and 10 were females. Their mean baseline plasma LDL-C level was 294 mg/dl, the triglycerides level was 155 mg/dl, and the HDL-C level was 44 mg/dl. The acute effect of therapy was to reduce the mean LDL-C levels by 58%.

The mean overall degree of stenosis for all coronary artery lesions decreased 1.9% from 32.5% +/- 16.0% standard deviation to 30.6% +/- 16.8% standard deviation (p=.0213). The stenosis of lesions less than or equal to 30% did not change significantly, while stenosis of lesions greater than 30% (n=103) showed a mean reduction of 4.3% over 2 years (p<0.001). The results in this group, with regard to change in lesion status based on an analysis of 187 coronary artery segments, are presented in Table 4.

Table 4
Coronary Angiography Results

Lesion Status**	H.E.L.P. Study (n = 187) (33 patients)		Group A and Group B (n = 95) (15 Patients)		Group C (n = 83) (16 Patients)	
	n	(%)	n	(%)	n	(%)
Regressed	50	26.7	18	18.9	31	37.3
No significant change (stable)	108	57.8	62	65.3	39	47.0
Progressed	29	15.5	15	15.8	13	15.7

n = the number of lesions.

** Cardiologists generally believe that an 8% or more increase or decrease in the size of a lesion, as measured by quantitative coronary angiography, is clinically significant. For this reason, the investigators, during the coronary angiography study of the H.E.L.P. System, defined lesion change as follows: ≥8% decrease in lesion stenosis as regression, a ≥8% increase in stenosis as progression, and <8% change as stable or no significant change.

4. Effect of Treatment on Other Blood Components

Table 5 presents the reductions seen in each subgroup for other plasma components.

Table 5
Mean and Range of Acute Percent Change in Other Plasma Components after Treatment

Component	Group A (4 patients)	Group B (32 patients)	Group C (30 patients)
Total Triglycerides	-47.4% (-90.1 to 100.0%) n = 395	-36.0% (-91.3 to 252.5%) n = 2359	-38.8% (-88.6 to 192.1%) n = 2335
Apolipoprotein A-1	-18.0% (-53.6 to 15.9%) n = 251	-18.7% (-58.2 to 47.7%) n = 376	-16.1% (-50.0 to 68.8%) n = 386
Apolipoprotein B	-61.0% (-84.1 to -29.7%) n = 251	-62.7% (-80.6 to -23.6%) n = 376	-52.5% (-73.9 to -3.9%) n = 387
Fibrinogen	-64.9% (-85.1 to -19.6%) n = 301	-58.7% (-95.3 to 23.3%) n = 2141	-57.5% (-98.2 to 271.4%) n = 2040

n = treatment number

These results indicate that there are significant reductions in total triglycerides, fibrinogen, and Apolipoprotein B. The reductions in Apo A-1 are similar to the reductions in HDL-C, since Apo A-1 is the major protein component of HDL-C. The results are generally consistent among the three subgroups.

Table 6 presents the mean acute percent change in other plasma components. LDL-C-apheresis is known to decrease the selected serum components listed below. The long-term effects of such reduction have not been established.

Table 6
Mean and Range of Percent Change in Other Plasma Components

Plasma Component	#Pts	#Treatments	Mean % Change After Treatment (Range)
HDL-C	91	6304	-13.6 (-89.2 to 382.4)
Fibrinogen	91	5519	-58.0 (-98.2 to 306.0)
Apolipoprotein A-1	40	1972	-16.8 (-61.0 to 68.8)
Apolipoprotein B	40	1968	-55.4 (-84.1 to -3.9)
Platelets	5	21	-10.1 (-46.0 to 55.3)
Ferritin*	5	19	-16.0 (-98.0 to 52.9)

* The acute reduction with treatment reported here was associated with an over time reduction in pretreatment ferritin levels from a baseline mean of 69.7 mg/dl to a mean at six months of 23.3 mg/dl in U.S. study patients.

Routine cellular and chemical studies indicated no clinically significant changes, with the exception of fibrinogen, plasma iron and ferritin. Although a review of the distribution of percentage change for fibrinogen indicates that several outliers may have occurred for this measure it should be noted that decreased levels of fibrinogen could be associated with bleeding, while increased levels could be associated with hypercoagulation. Decreases in plasma iron and ferritin levels, with an increase in iron-binding capacity, indicated the development of mild iron deficiency. Although no evidence of significant anemia developed, patients' ferritin and iron levels should be monitored while on H.E.L.P. therapy and corrective measures taken as appropriate.

Acute changes in complete blood count (CBC) and in blood chemistry parameters are presented in Tables 7 and 8. These changes were measured during the first 4 treatments for the first 5 patients in the U.S. study and periodically for patients in the German study.

Table 7
Mean and Range of Acute Percent Changes in CBC

Component	Mean Change (%)	Range of Change (%)
Hematocrit	-3.3	-20.4 to 117.1
Hemoglobin	-3.8	-54.7 to 15.7
WBC Count	17.7	-50.8 to 98.3
Granulocytes	5.1	-48.0 to 52.6
Lymphocytes	-3.0	-61.1 to 123.8
Other	6.6	-100.0 to 400.0
Platelet Count	-10.1	-46.0 to 55.3

Table 8
Mean and Range of Acute Percent Changes in Blood Chemistry

Parameter	Mean Change (%)	Range of Change (%)
Total Protein	-18.8	-29.6 to -8.1
Albumin	-15.5	-26.2 to -6.5
Sodium	0.7	-1.5 to 2.9
Potassium	0.9	-9.5 to 13.9
Carbon Dioxide	7.8	-11.5 to 25.0
Chloride	3.5	0.9 to 6.9
Calcium	-6.3	-13.1 to -2.2
Phosphorus	2.0	-17.9 to 22.2
Bilirubin	19.1	-20.0 to 100.0
Alk. Phosphatase	-12.4	-21.0 to -6.0
LDH	-7.2	-66.5 to 81.5
SGOT	-11.6	-23.3 to 16.7
GGPT	-25.5	-50.0 to -8.3
CPK	-43.2	-56.5 to -33.0
Glucose	-5.6	-55.8 to 25.0
BUN	-11.5	-23.1 to 0,0
Creatinine	-12.3	-22.2 to 0.0
Uric Acid	-18.8	-28.3 to -6.9

These data indicate varying degrees of acute changes in these parameters with treatment, although none of these changes are considered clinically significant.

Chronic changes over the course of 6 months of weekly therapy were reviewed and, although immunoglobulin levels remained stable, decreases in plasma iron and ferritin levels with an increase in iron-binding capacity were observed. These changes indicated that development of mild iron deficiency may have occurred. These data are presented in Table 9.

Table 9
Pre-Treatment Mean Levels Over 6 Months of Weekly Therapy

Treatment	Plasma Iron (μg/dL)		TIBC (μg/dL)		Ferritin (mg/dL)	
		Range		Range		Range
1	81.0	8-245	354.2	245-491	69.7	9-165
5	80.0	29-193	371.1	291-515	47.6	1-137
9	76.6	15-127	381.0	306-506	37.1	5-96
13	68.7	21-173	381.0	256-519	26.3	4-87
17	68.1	17-178	389.6	216-528	25.1	1-72
21	63.2	24-130	389.5	288-501	21.6	5-60
6 Months	71.6	7-196	413.9	342-519	23.3	6-66

5. Complications and Adverse Events

Complications reported in patients on H.E.L.P. therapy are those associated with extracorporeal therapy, including access problems, hypotension, chills, headache, fatigue, nausea, and swelling of hands and face. For the purpose of providing complete safety information, complications reported through October 1995 from all of the U.S. study patients (2,826 treatments in 40 patients) and through 1995 from all German patients treated at the H.E.L.P. centers that participated in the clinical study (21,306 treatments in 136 patients - 51 original German patients and additional 85 patients treated at the German H.E.L. P. centers after the study was completed) are provided below. Table 10 presents the events reported in U.S. patients and Table 11 presents events reported in German patients.

Table 10
Complications Summary For All U.S. Patients

Complication	U.S. STUDY (n=40 pts) (2,826 treatments)		
	Total No. of Events		Total No. of Patients Reporting the Complication
	n	(%)	n
Venous Access Problem*	66	2.3	20
Hypotension	27	1.0	16
Fatigue	8	0.3	8
Chills/Shivering	9	0.3	7
Prolonged PTT or ACT**	7	0.2	5
Nausea/Vomiting	7	0.2	7
Chest Heavy/Pain	4	0.1	2
Dizziness/Syncope	4	0.1	4
Headache	4	0.1	4
Elevated Temperature	3	0.1	3
GI Bleed	2	<0.1	2
Flushing	1	<0.1	1
Hyperventilation	1	<0.1	1
Wheezing	1	<0.1	1
Elevation of Liver Enzymes	1	<0.1	1
Apical Density on CXR	1	<0.1	1
Ankle Swelling	1	<0.1	1
Prostatitis	1	<0.1	1
Hematuria	1	<0.1	1
Hypoglycemia	1	<0.1	1
Sympathetic Reflex Dystrophy	1	<0.1	1
Angina/2nd PTCA	1	<0.1	1
Endarterectomy	1	<0.1	1
Total	153	5.4	30

* Types of venous access problems encountered: complete inability to gain venous access due to clotted fistula, collapsed or sclerosed veins, small or inadequate vein; infiltration of fluid or blood at the needle site; clot in the needle; inability to cannulate; pain and/or burning at needle site; high venous pressure due to partial obstruction within the needle; needle aperture placement against wall of vein; or spasm of vein; and lack of patient cooperation.

** Includes reports on patients who had heparinized CV lines through which blood samples were drawn.

Table 11
Summary of Complications for All German Patients

Complication	21,306 treatments		
	Total No. of Events		Total No. of Patients Reporting the Complication
	n	(%)	n
Swelling Face and Hands	222	1.04	15
Angina Pectoris	218	1.02	33
Fatigue	208	0.98	33
Headache	169	0.79	27
Venous Access Problems*	112	0.53	68
Hypotension	111	0.52	41
Eyes Burning	97	0.46	17
Vertigo	88	0.41	34
Nausea	76	0.36	39
Coldness/Shivering	70	0.33	25
Muscle, Bone and Joint Pain	49	0.23	18
Gastrointestinal Complaints	42	0.20	19
Sweating	41	0.19	17
Missed Puncture	37	0.17	26
Bradycardia	37	0.17	16
Collapse	37	0.17	24
Dysphagia	30	0.14	8
Disturbed Cutaneous Sensitiveness	28	0.13	10
Other Problems	28	0.13	14
Fever/Elevated Body Temperature	21	0.10	15
Hypertension	21	0.10	14
Arrhythmia	18	0.08	12
Hematoma	18	0.08	13
Emesis	14	0.07	11
Allergic Reaction Local (Flush)	14	0.07	4
Allergic Reaction Systemic	13	0.06	6
Dyspnea	13	0.06	8
Insomnia	13	0.06	3

Table 11

Complications Summary for All German Patients (continued)

Complication	21,306 treatments		
	Total No. of Events		Total No. of Patients Reporting the Complication
	n	(%)	n
Hemolysis	12	0.06	10
Tachycardia	11	0.05	9
Prolonged Bleeding Time	11	0.05	11
Edema	11	0.05	7
Shunt Occlusions	9	0.04	7
Restlessness	9	0.04	6
Cough	9	0.04	4
Bleeding	8	0.04	4
Polyuria	8	0.04	7
Hypoglycemia	5	0.02	4
Hyperventilation	2	0.01	2
Other Rhythm Problems	1	0	1
Total	1904	8.94	642

* The venous access problems that occurred were puncture pain, missed puncture, needle thrombosis, needle dislocation, and other puncture problems.

6. Myocardial Infarctions

There were no nonfatal myocardial infarctions (MIs) in the U.S. study; nonfatal MIs were not recorded in the German study. One U.S. and 5 German patients had fatal MIs during the study.

Table 12

Myocardial Infarctions Summary

	U.S. study	German study
nonfatal myocardial infarctions	0	not recorded
fatal myocardial infarctions	1	5

7. Deaths

A total of six deaths (five in Germany, one in the U.S.) out of the 91 patients, were reported during the clinical study reported in the PMA. These are listed and described in Table 13. All of the patients died of cardiovascular disease.

In addition to the 6 deaths that were reported above, Braun reported subsequent patient deaths that occurred in both Germany and the United States. In Germany, where the device is currently marketed, Braun reported a total of 27 deaths out of 441 patients. In the United States, Braun reported one additional death of a patient not included in the PMA cohort.

None of the deaths were considered to have been related to treatment with the H.E.L.P. System. However, it cannot be concluded with certainty, due to the small size of the patient groups and the lack of a control group, whether any of the deaths were treatment related.

Table 13
Patient Deaths

Patient			History		HELP Treatment			Death Information		
Patient No.	Age	m/f	CHD/OAD	Infarction	Start Date	Interval	Date and No. of Last	Date of Death†	Cause	Autopsy
German Study										
002007* 2, Pt. 7	70	f	3-vessel CHD; CABG; shunt implant; PTCA		3/12/87	weekly	9/27/91 145th	10/2/91 (5)	Ischemia colitis, Pericardial hemorrhage and tamponade	Y
004042* 4, Pt. 42	50	m	CHD	Infarction	12/23/87	weekly	11/21/88 49th	11/21/88 (0)	Acute cardiac death (failure of heart and circulation)	N
005025** 5, Pt. 25	40	m	3-vessel CHD	Recurrent anterior and posterior wall infarction	1/26/88	weekly	4/17/89 53rd	5/1/89 (14)	Acute left ventricular insufficiency with cardiogenic shock; reinfarction suspected.	N
007033** 7, Pt. 33	33	f	3-vessel CHD; CABG 3x	Posterior wall infarction	1/16/87	weekly	4/30/87 14th	5/3/87 (3)	Recurrent cardiac infarction due to thrombosis known ventricular arrhythmia, severe CHD	Y
008038* 1, Pt. 38	47	m	3-vessel CHD; CABG; aneurysm; surgery	Infarction	5/12/87	biweekly	2/5/91 109th	2/16/91 (11)	Myocardial infarction/cardiogenic shock; coronary thrombotic occlusion of the main artery	Y
U.S. Study										
445-460*	47	m	CHD; angina; CABG	Infarction	2/18/91	weekly (q 6m) biweekly (>6 mos)	7/5/93 72nd	7/13/93 (8)	Acute anterior wall myocardial infarction	N

Abbreviations:
- CHD: Coronary Heart Disease
- CABG: coronary arterial bypass grafting: Aortocoronary Venous Bypass
- PTCA: Percutaneous Transluminal Coronary Angioplasty

† Days after the last HELP treatment in parentheses
* Patients in Group C
** Patients in Group B

8. Patient Accountability

The following table shows, by subgroup, the number of patients who discontinued participating in the study.

Table 14
Patients discontinuing treatments

	Enrolled	Discontinued before 6 months	Discontinued between 6-24 months
Group A	4	0	0
Group B	32	4	4
Group C	30	1	6
Other	25	4	6
Total	**91**	**9**	**16**

Prior to 24 months, 3 of the 25 patients who discontinued, died. An additional 3 patients discontinued participating in the study due to access problems, and the remaining 19 patients discontinued due to miscellaneous or unknown problems. Sixty-six patients remained in the study at 24 months.

Modified H.E.L.P. System:

Since the submission of the PMA and the subsequent advisory meeting of the Gastroenterology/Urology Panel, held on April 21, 1995, there have been several modifications to the H.E.L.P. System. The modifications include the following:

1. Heparin adsorber (and preservation solution)

Instead of using two 250 ml heparin adsorbers, Braun switched to one 500 ml heparin adsorber. Although there was no change of materials in the adsorber, Braun did change the preservation solution used in the adsorber. Originally Braun used a 0.9 percent sodium chloride solution in the adsorber which was added prior to steam sterilization of the component. Upon testing of the eluate of the stored column, a hemolytic substance was discovered. In the original device, large saline

washes were necessary to remove the hemolytic substance prior to use of the device on patients By switching to a sodium acetate (pH 5.12) buffer as the preservation solution Braun has had no further problems with the formation of any hemolytic substances.

In 1991, Braun began to use this modification to the H.E.L.P. System in Germany. Use of this modification to the device was not begun until 1995, in the U.S.

2. **Precipitate filter**

The original precipitate filter was a single layer support. Braun is now modifying their H.E.L.P. System to use the Corning Costar QRII-M filter with a double layer support. They began to use this modification of the H.E.L.P. System in Germany in 1993. Use of the modified precipitate filter was not begun in the U.S. until 1995.

Braun has provided results, from patients in both Germany (3,826 treatments) and the U.S. (87 treatments), to demonstrate the safety and effectiveness of this change. From the data provided it does not appear that the use of a double layer support alters the ability of the H.E.L.P. System to remove LDL-C. In addition, no new adverse events/complications or substantial changes to the rates of occurrence of the adverse events were seen using the modified precipitate filter.

3. **Blood tubing**

There are a number of modifications to the blood tubing set. The modified device now uses only 9 blood/fluid lines while the original device used 11 (deleting the use of a Y connector and a line which connected to an empty bag). The material used in the housing of the transducer protectors included in the arterial, plasma, circulation, filtrate pump, substitution pump, and venous lines has been changed from styrene acrylonitrile copolymer to polyvinyl chloride (PVC). There have also been vendor changes for other tubing materials. Finally, the tubing sets will now be manufactured by B. Braun Carex (Mirandola, Italy).

Biocompatibility testing including cytotoxicity, intracutaneous implantation, subchronic toxicity, systemic toxicity, hemocompatibility with plasma including complement activation, PT, PTT and fibrinogen testing, skin sensitization and irritation, and mutagenicity were performed. Testing showed the materials to be safe for use in the device.

4. Dialyzer membrane

Braun used the Secon UF ultrafilter , a hollow fiber cuprophane membrane, in its original device. They are now using the Toray Filtryzer BI-1.3H (510(k) K935471), which uses a polymethylmethacrylate membrane (PMMA). The Toray Filtryzer is only used as a modification to the H.E.L.P. System in the U.S. It has not been used as a modification to the H.E.L.P. System in Germany.

As the marketed Toray Filtryzer is only indicated for use in hemodialysis treatment of patients with chronic or acute renal failure, additional testing was performed and results provided by Braun. These tests included structural and mechanical integrity of the filter at low pH, cytotoxicological tests for leaching of toxins, and tests to determine protein loss across the membrane. Tests demonstrated that the filter performed its intended function under the new conditions.

Braun has provided data from patients in the U.S. (82 treatments) to demonstrate that the safety and effectiveness of this modification to the H.E.L.P. System does not change substantially from that seen in the original device.

Due to the small amount of data provided to demonstrate the safety and effectiveness of all modifications to the H.E.L.P. System, certain clinical laboratory assessments will be made before and after treatments for the first 900 treatments of a post-approval study (see XIII Approval Specification below). After the first 900 treatments the same data will be provided annually.

X. CONCLUSIONS

The laboratory and clinical data submitted on the H.E.L.P. System support the safety and effectiveness of the system for the treatment of hypercholesterolemia in the populations for whom treatment is indicated. The data support the following conclusions:

1. Acute reductions in LDL-C ranging from 95.2% to 5.0% (mean 60% to 64%) and in total cholesterol ranging from 76.2% to 2.0% (mean 49% to 57%) in the three subgroups occurred. LDL-C levels return to baseline levels in a non-linear fashion over a 14 day period with a return to 50% of pretreatment levels by a mean of 4.67 days.

2. Acute changes in HDL-C levels which were reported in the study, ranged from reductions of up to 89.2%, to gains of up to 382.4%. The increases in HDL-C levels seen immediately post-treatment in the study are due to heparin administration

which is known to produce, transiently, lipoproteins which may appear to be HDL-C , but are not true HDL-C. Many patients with hypertriglyceridemia will have HDL-C levels immediately post-H.E.L.P. therapy measuring higher than they actually are. These proteins disappear gradually after heparin in the plasma is metabolized. This effect occurs *in vivo* and even in the test tube after the blood is drawn. This phenomenon has been known for decades and is considered harmless to the patient.[10-15] The distribution of HDL-C values post-H.E.L.P. therapy suggests that the majority of patients have a 12% to 17% reduction in their HDL-C levels. It should be noted that, since epidemiological studies have shown that both low HDL-C and high LDL-C are independent risk factors for coronary heart disease, the risk of acutely lowering of HDL-C while lowering LDL-C is unknown.

3. Acute reduction in ApoB and total triglycerides were similar to reduction in LDL-C.

4. Hematological and chemistry profiles were not substantially changed by H.E.L.P. therapy, except for fibrinogen (-58%) , iron (-21%), and ferritin (-16%). While a review of the distribution of percentage change for fibrinogen indicates that several outliers may have occurred for this measure, it should be noted that decreased levels of fibrinogen could be associated with bleeding, while increased levels could be associated with hypercoagulation. Changes in iron laboratory assays over time indicate the development of mild iron deficiency. Although no evidence of significant anemia developed, patients' ferritin and iron levels should be monitored while on H.E.L.P. therapy and corrective measures taken as appropriate.

5. The primary adverse events which may be expected include, vascular access problems, hypotension, nausea, chills, fatigue, angina and headache.

6. Therapy with this device has not been demonstrated to diminish the need for cardiovascular interventional procedures such as CABG, PTCA or endarterectomy.

7. The clinical studies using the H.E.L.P. System were not designed to address and did not establish any long-term clinical benefits of acute lowering of LDL-C with this device.

XI. PANEL RECOMMENDATIONS

At an advisory meeting held on April 21, 1995, the Gastroenterology/Urology Devices Panel recommended that B. Braun of America's PMA for the H.E.L.P. System be

approved subject to submission to, and approval by the Center for Devices and Radiological Health (CDRH) of the following:

1. Labeling

   a. The device is to be indicated for the following patient populations:

      Group A Functional Hypercholesterolemic Homozygotes with LDL-C > 500 mg/dl;

      Group B Functional Hypercholesterolemic Heterozygotes with LDL-C ≥ 300 mg/dl; and

      Group C Functional Hypercholesterolemic Heterozygotes with LDL-C ≥ 200 mg/dl and documented coronary heart disease.

   b. Only claims for acute lowering of LDL-C are to be included in the labeling. Claims of time-averaged or chronic lowering imply a clinical benefit that was not demonstrated in this trial.

2. Post-Approval Study

   All patients treated with this device will be enrolled in a registry and monitored. At this time, the study is open ended (see Section XIII Approval Specification).

3. Physician/Technical Personnel Training

   All physicians and technical persons providing therapy with the device will receive training prior to using the device.

4. Patient Information Brochure

   Patients will be fully informed of the risks and benefits of this therapy through a Patient Brochure.

XII. CDRH DECISION

CDRH concurred with the recommendations of the Panel. Although there is a lack of data presented in the PMA to demonstrate the long-term benefits of lowering LDL-C using the H.E.L.P. System, there are numerous literature articles[1-9] which support the link between lowered LDL-C levels and a reduced risk of heart disease and coronary

events. Patients in the three groups (A, B and C), described in the indications for use, are considered to be at extreme risk for CHD due to their elevated LDL-C levels and their inability to reduce their LDL-C to recommended levels[5] using combined diet and drug therapies. Acute lower of LDL-C by the H.E.L.P. System can be considered a clinical benefit for these 3 special patient populations. No other clinical benefit (e.g., reduction/prevention of coronary heart disease) due to lowering of LDL-C with the device has been demonstrated and therefore, no claims for any other benefit (e.g., reduction/prevention of CHD) can be made at this time.

FDA inspection determined manufacturing facilities to be in compliance with the Good Manufacturing Practices Regulation.

CDRH issued an approval order for the application on SEP 19 1997.

XIII. APPROVAL SPECIFICATIONS

Directions for Use: See attached Labeling (Attachment A).

Patient/Registry/Post-approval Study requirements and restrictions: the sponsor has agreed to conduct a patient registry/post-approval study for all patients using the device. The patient registry/post-approval study will be conducted in two parts. The first part of the study encompasses the first 900 treatments with the device and is intended to gather additional safety and effectiveness data of the following component modifications:

- precipitation filter;
- heparin adsorption filter;
- dialysis filter; and
- tubing set.

The second part of the study is open-ended and is a continuation of the post-approval study of safety and effectiveness of the device. Patient data for the entire (parts 1 and 2) study is to be collected and a report generated and submitted annually to FDA for review. This report will include a summary of adverse events, morbidity and mortality statistics, analysis of blood lipid and chemistry laboratory results and summary statistics on demographics and other baseline characteristics of registry patients. In addition to the annual report, all patient deaths are to be reported to the FDA within 10 days after

the applicant receives or has knowledge of information concerning a death. The mortality statistics are to be submitted on a quarterly basis and will include all patient information for patients who have died, whether the death is related or unrelated to the device. The timely reporting of such events is necessary due to the limited device experience. The quarterly reports will continue until FDA determines this reporting frequency is no longer needed.

Expiration dating for the following components of the device has been established and approved: 5 years for the H.E.L.P. blood line set, 5 years for the H.E.L.P. Precipitate Filter, 2 years for the H.E.L.P. Heparin Adsorber 500 , 2 years for the H.E.L.P. Ultrafilter and 18 months for the H.E.L.P. Plasmapheresis Filter.

Expiration dating for the following accessory solutions/concentrates which are compounded by B. Braun Melsingen have been established and approved: 3 years for the heparin sodium solution and the acidic bicarbonate hemodialysis concentrate, 1.5 years for the 0.9% sodium chloride solution and the sodium acetate buffer solution, and 1 year for the alkaline bicarbonate hemodialysis concentrate.

The sale distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii), (1) insofar as the labeling specify the requirements that apply to the training of practitioners who may use the device as approved in the order and (2) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

Warning, hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions and Adverse Reactions in the attached labeling.

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IMPORTANT INFORMATION FOR THE H.E.L.P. SYSTEM

TABLE OF CONTENTS

H.E.L.P. SYSTEM™ COMPONENTS AND ACCESSORIES

The H.E.L.P. (Heparin-induced Extracorporeal Lipoprotein Precipitation) System consists of the following six components: (1) Plasmat-secura™; (2) Haemoselect™ Plasma Filter; (3) precipitate filter; (4) heparin adsorber 500; (5) Toray Filtryzer™ B1-1.3H; and (6) H.E.L.P. System line set.

PRINCIPLES OF OPERATION

H.E.L.P. therapy is a treatment for lowering total blood cholesterol as well as low density lipoprotein (LDL) cholesterol levels by direct removal from the blood stream. The procedure requires venous (vein to vein, arterial venous fistula, or central venous) access, and as blood is removed, plasma and red blood cells are separated by a 0.55 micron polypropylene hollow fiber filter. The plasma is then mixed in the precipitate chamber with a sodium acetate buffer (pH 4.85) containing 100 units per ml of heparin to achieve a final pH of 5.12. The resultant precipitates containing cholesterol particles are removed by filtration through a 0.45 micron polycarbonate filter. The excess heparin in the filter is adsorbed by a DEAE cellulose filter. The plasma is then passed through the ultrafilter where the pH is restored through bicarbonate dialysis and excess fluid is removed through ultrafiltration before the treated plasma with the blood cells from the plasma is mixed with the blood cells from the plasma filter and returned to the patient. The procedure takes about 1.5 hours.

The H.E.L.P. System is controlled through a function processor (protective system 1) and a control processor (protective system 2). The task of the function processor is to control all the procedures necessary for the operation of the device. Furthermore, it monitors the limit values and enables communication with the operator. That is, the values put in by the operator via the keyboard are translated into nominal values for the controls, valves, etc., assigned to it. The task of the control processor is to monitor the function processor for correct alarm reactions. It receives the keyboard inputs at the same time as the function processor, thus enabling it to follow the input data of the operator completely independently.

1.0 Description

The H.E.L.P. System is an extracorporeal blood processing system that consists of three groups of components (the Plasmat-secura, the disposable H.E.L.P. filter set, and the disposable H.E.L.P. blood line set) and the extracorporeal solutions used in treatment.

The first of these components is the system hardware and software, called the Plasmat-secura, which controls the pumps that regulate the flow of blood from and to the patient, and controls and monitors blood and plasma in the extracorporeal circuit. The Plasmat-secura consists of the mobile base frame, which is on wheels, and the following four separate compact modules that are placed on top of the module base frame: dialysate, cascade, blood, and communications. The Plasmat-secura segments its various functions and assigns them to one of three microprocessors. The first microprocessor system, referred to as the function processor, controls and monitors the entire operation of the device. The second microprocessor system, the control processor, monitors the function processor to ensure proper response to potentially hazardous events. The third microprocessor system, the monitoring display processor, provides status information.

The second component is the H.E.L.P. filter set, consisting of four single use filters through which the blood or plasma are carried extracorporeally during treatment. Each filter in the series is a sterile disposable filter intended for single use only. The HAEMOSELECT® 0.55 micron plasmapheresis filter is a conventional hollow fiber polypropylene plasmapheresis filter that separates the whole blood into a plasma fraction and a plasma poor, cell enriched fraction. The polycarbonate precipitate filter separates the LDL cholesterol/heparin aggregates from the patient's plasma. The DEAE Adsorber, the third filter in the series, acts as an ion exchanger and removes the excess heparin from the plasma. The H.E.L.P. ultrafilter is a conventional hollow fiber polymethylmethacrylate dialyzer used for bicarbonate hemodialysis. During this final filtration process, the added acetate buffer solution is removed from the plasma and physiological pH is restored.

The third component is the H.E.L.P. line set, which is comprised of nine blood lines. All components are manufactured by injection molding of standard PVC plastic material. The lines are sterile and disposable, and are intended for single use only.

<u>Caution:</u> Federal law restricts this device to sale by or on the order of a physician with appropriate training.

This system may be used only as prescribed by a licensed and appropriately trained physician. While connected to the extracorporeal system, the patient must be attended to at all times by a physician or a qualified health-care professional adequately trained in all aspects of the procedure. All physicians and medical personnel utilizing the H.E.L.P. System will be required to have completed an appropriate training program. Each patient treated with the system must be enrolled in a Patient Registry prior to the initiation of treatment. Physicians using the device will be required, through the Patient Registry, to periodically report specified patient data regarding the treatments. Due to the continuing need to update information about therapy with the H.E.L.P. System, devices will only be sold to physicians who have agreed to participate in the follow-up Patient Registry. Physicians who do not comply with the Patient Registry reporting requirements will not be permitted to purchase additional disposable devices.

2.0 Indications for Use

The H.E.L.P. (Heparin-induced Extracorporeal Lipoprotein Precipitation) System is indicated for use in performing low density lipoprotein cholesterol (LDL-C) apheresis to acutely remove LDL-C from the plasma of the following high risk patient populations for whom diet has been ineffective and maximum drug therapy has either been ineffective or not tolerated:

Group A	Functional Hypercholesterolemic Homozygotes with LDL-C > 500 mg/dl
Group B	Functional Hypercholesterolemic Heterozygotes with LDL-C ≥ 300 mg/dl; and
Group C	Functional Hypercholesterolemic Heterozygotes with LDL-C ≥ 200 mg/dl and documented coronary heart disease (CHD).

Documented CHD is defined as having one or more of the following:

- a prior documented myocardial infarction (MI);
- a prior coronary artery bypass graft surgery (CABG);
- a prior percutaneous transluminal coronary angioplasty (PTCA) with or without atherectomy or coronary artery stent placement;
- significant angina pectoris with a positive thallium or other heart scanning stress test.

Patients are eligible for H.E.L.P. therapy if, after a minimum of a six-month trial of an American Heart Association (AHA) Step II diet (or equivalent) and maximum tolerated combination drug therapy designed to reduce LDL-C, they fall into Groups A, B, or C as defined above. In order to determine if a patient fits the LDL-C requirements of any of the groups (A, B, or C), baseline LDL-C levels need to be determined while patients are continuing on their diet and drug therapies. A baseline LDL-C level is obtained by calculating the mean value of three serum samples obtained over a period of 2-4 weeks and collected after the patient has fasted overnight. All LDL-C values should be within 10% of each other, indicating a stable condition. If a patient's diet or drug therapy is modified a new baseline LDL-C should be established. Maximum tolerated combination drug therapy is defined as an adequate trial of drugs from at least two separate classes of hypolipidemic agents such as anion exchange resins/bile acid sequestrants, 3-hydroxy-3methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, fibric acid derivative, or niacin/nicotinic acid.

Although clinical benefit of LDL-C lowering has been documented in several diet, drug and/or surgical intervention trials, clinical studies using the H.E.L.P. System were not designed to address and did not establish the long-term clinical benefit of acutely lowering LDL-C.

3.0 Contraindications

LDL apheresis with the H.E.L.P. System is contraindicated in patients:

(a) for whom the use of heparin would cause excessive or uncontrolled anticoagulation or for whom adequate anticoagulation cannot be safely achieved, such as patients with hemophilia or patients who have had recent surgery; or

(b) with known hypersensitivity to heparin or ethylene oxide.

4.0 Warnings

1. The safety of LDL-apheresis treatment with the H.E.L.P. System occurring more than once a week or for treated volumes larger than one plasma volume has not been determined.

2. Before using the H.E.L.P. System, carefully review the Operator's Manual. Persons performing the procedures must be qualified and have completed the required training program. Users should follow all operating or maintenance procedures published by B. Braun Medical Inc. To do otherwise, may result in injury or loss of life.

3. Prior to initiating an LDL-apheresis procedure, carefully review the package inserts for all disposables and other materials to be used during the procedure. Failure to comply strictly with such package inserts, including the instructions for use, may result in serious injury to or possible death of patients.

4. Use special caution in patients where the extracorporeal volume of approximately 400 ml potentially will exceed 10% of the patient's blood volume. Such patients are at higher risk of experiencing hypovolemia, which is sometimes followed by hypotension.

5. Rinse and prime the fluid pathway of the disposable components of the H.E.L.P. System, especially the Heparin Adsorber, with sufficient volume of appropriate solutions before commencing the procedure. Because air bubbles in the disposables may lead to complications such as coagulation of plasma and impairment of performance, give full attention to measures that will prevent air bubble migration into the disposables during rinsing and priming.

6. LDL-apheresis treatment of patients who have taken any diuretics or antihypertensive drugs within 24 hours of treatment may cause hypotension in such patients. When clinically feasible, patients should not receive diuretics or antihypertensive drugs during the 24 hour period prior to undergoing the LDL-apheresis procedure. Before each treatment, physicians should determine when patients took their last dose of such medication.

7. Before each treatment, the physician should determine the patient's state of hydration by physical exam and history. Record fluid intake for the 24 hour period preceding H.E.L.P. treatment. Determine whether the patient has experienced any unusual fluid loss, *e.g.*, bleeding, vomiting, diarrhea, excessive urination, or reduced fluid intake related to gastrointestinal upset, the common cold, allergies, or other causes, within the 24 hour period prior to treatment. If the patient is dehydrated, the patient may experience hypotension during H.E.L.P. therapy.

8. Proper cleaning and disinfectant procedures, as described in the H.E.L.P. System Operator's Manual must be followed after each treatment. Failure to do so may result in transmission of disease from patient to patient or in an increase in patient infections.

9. During an LDL-apheresis procedure, an acetate buffer solution, a heparin sodium solution, a 0.9% sodium chloride solution, an acidic

bicarbonate hemodialysis concentrate HDY 320, and a 5% bicarbonate concentrate are used. Carefully identify each solution and ensure that it is properly connected to the H.E.L.P. System. Using the incorrect solution may result in serious injury or possible death.

10. No chemical or solvents are to be used either inside or outside of the disposables.

5.0 Precautions

1. The long-term safety and efficacy of LDL-apheresis using the H.E.L.P. System have not been established.

2. The safety and efficacy of LDL-apheresis using the H.E.L.P. System have not been established for pregnant women or for women during the lactation period, e.g., the effect of treatment on folic acid levels has not been determined.

3. The safety and efficacy of LDL-apheresis using the H.E.L.P. System have not been established for the following: (1) patients less than 106 lbs or 48.2 kg in body weight; (2) patients less than 15 years of age; (3) patients with certain cardiac impairments such as congestive heart failure, major arrhythmia, or diastolic blood pressure greater than 100 mmHg on two separate occasions at least four hours apart; (4) patients with renal insufficiency (creatinine greater than 2.0 mg/dl); (5) patients with untreated hypothyroidism; (6) patients with uncontrolled diabetes mellitus; (7) patients with fasting triglycerides greater than 500 mg/dl; (8) patients whose weight is greater than 1.5 times their ideal weight; (9) patients with malignancy; (10) patients with a positive test for acute hepatitis or HIV, including patients with AIDS; and (11) patients whose immune system is suppressed.

4. LDL-apheresis should be considered a lifetime therapy since, upon discontinuation of therapy, lipid levels will return to pre-treatment levels or higher. Diet and drug therapy must be maintained during the treatment period as the rate of rebound will accelerate if lipid-lowering drug therapy is discontinued.

5. The filters and blood line set are disposable and are **intended for use in a single procedure only. Never reuse.** Discard the disposables after each procedure.

6. Physicians and operators should follow the OSHA and the CDC/ACIP Adult Immunization Guidelines for Hemodialysis Patients. It is recommended that patients be screened for Hepatitis B and other

infectious diseases; however, due to possible exposure to hepatitis virus, human immunodeficiency virus, and other infectious agents when handling extracorporeal blood circuits, blood or blood products, universal precautions should be taken at all times to prevent the exposure to and transmission of such agents.

7. When disposing of the disposable device components and wastes, comply with all local requirements and the policy of the facility regarding precautions for and prevention of infection and environmental pollution.

8. Medical personnel should monitor the patient for adverse symptoms at all times during treatment and should be trained as to the protocol for responding with appropriate interventions. (See Section 6.1, Notes for Potential Adverse Reactions.)

9. Closely monitor patient clotting time periodically during the procedure to ensure that an adequate level of anticoagulation is maintained.

10. Patients' lipid levels (total cholesterol, triglycerides, LDL-C, and HDL-C) should be monitored every three months during the course of long-term therapy. Samples for cholesterol levels should be taken immediately before and after a given LDL-apheresis procedure.

11. High density lipoprotein cholesterol (HDL-C) may be acutely reduced by up to 17% post-treatment. Epidemiologic studies have shown that both low HDL-C and high LDL-C are independent risk factors for coronary heart disease. The risk of acutely lowering HDL-C while lowering LDL-C with this device is unknown.

12. Instructions for heparin administration should be followed as stated in the guidance provided in the Instructions for Use for the H.E.L.P. System. The amounts of heparin outlined in the Instructions for Use are intended as general suggestions. The exact amount, frequency and method of administration of heparin are the sole responsibility of the prescribing/attending physician and should be selected based on the individual patient's clinical condition.

13. All connections of the extracorporeal circuit should be checked carefully prior to initiating and during the procedure. Avoid kinking of the tubing lines and the patient's vascular access devices at all times.

14. Drip chambers in the extracorporeal circuit should be kept at least 2/3 to 3/4 full and monitored at all times in order to decrease the risk of air embolism.

15. The fluid circuit of this system is intended to be sterile and nonpyrogenic. Aseptic handling techniques are necessary to maintain these conditions. Check the packaging for the disposable device components to ensure that it is intact. Do not use a disposable product if the package, sterile bag, protective cap or the product itself is damaged. Do not open the sterile bags containing the disposables until use.

16. In transporting and storing the device components, handle with care and store all disposables in a clean and secure area at room temperature (5-30°C), avoiding exposure to direct sunlight, high humidity or excessive vibration. Do not allow the H.E.L.P. Heparin Adsorber or the ultrafilter to freeze. Do not use components which may have been damaged or frozen.

17. Only components supplied by B. Braun (i.e., B. Braun's disposables) can be used with the H.E.L.P. System.

18. During the clinical study, decreases in plasma iron and ferritin levels with an increase in iron-binding capacity indicated the development of mild iron deficiency. Although no evidence of significant anemia developed, patients' ferritin and iron levels should be monitored while on H.E.L.P. therapy, and corrective measures taken as appropriate.

19. In case of power failure or system shutdown, terminate the procedure immediately according to the instruction provided in the Operator's Manual for the H.E.L.P. System.

6.0 Adverse Events

Complications reported through October 1995 from all of the U.S. clinical study patients (2,826 treatments in 40 patients) and through 1995 from all German patients treated at the H.E.L.P. centers that participated in the clinical study (21,306 treatments in 136 patients) are provided below. Table 1 presents the events reported in U.S. patients and Table 2 presents events reported in German patients.

Table 1
Adverse Event Summary
For All U.S. Patients

Adverse Event	U.S. STUDY (n=40 pts) (2826 treatments)		
	Total No. of Events		Total No. of Patients Reporting the Complication
	n	(%)	
Venous Access Problem 1/	66	2.3	20
Hypotension	27	1.0	16
Chills/Shivering	9	0.3	7
Fatigue	8	0.3	8
Prolonged PTT or ACT*	7	0.2	5
Nausea/Vomiting	7	0.2	7
Chest Heavy/Pain	4	0.1	2
Dizziness/Syncope	4	0.1	4
Ache	4	0.1	4
Elevated Temperature	3	0.1	3
GI Bleed	2	<0.1	2
Flushing	1	<0.1	1
Hyperventilation	1	<0.1	1
Wheezing	1	<0.1	1
Elevation of Liver Enzymes	1	<0.1	1
Apical Density on CXR	1	<0.1	1
Ankle Swelling	1	<0.1	1
Prostatitis	1	<0.1	1
Hematuria	1	<0.1	1
Hypoglycemia	1	<0.1	1
Sympathetic Reflex Dystrophy	1	<0.1	1
Angina/2nd PTCA	1	<0.1	1
Endarterectomy	1	<0.1	1
Total	153	5.4	30

* Includes reports on patients who had heparinized CV lines through which blood samples were drawn.

1/ Types of venous access problems encountered: complete inability to gain venous access due to clotted fistula, collapsed or sclerosed veins, small or inadequate vein; infiltration of fluid or blood at the needle site; clot in the needle; inability to cannulate (technician error); pain and/or burning at needle site; high venous pressure due to partial obstruction within the needle, needle aperture placement against wall of vein, or spasm of vein; and lack of patient cooperation.

Table 2. Adverse Event Summary
For All German Patients (n = 136)

Adverse Event	21306 treatments		
	Total No. of Events		Total No. of Patients Reporting the Complication
	n	(%)	
Swelling Face and Hands	222	1.04	15
Angina Pectoris	218	1.02	33
Fatigue	208	0.98	33
Headache	169	0.79	27
Venous Access Problems 2/	112	0.53	68
Hypotension	111	0.52	41
Eyes Burning	97	0.46	17
Vertigo	88	0.41	34
Nausea	76	0.36	39
Coldness/Shivering	70	0.33	25
Muscle, Bone and Joint Pain	49	0.23	18
Gastrointestinal Complaints	42	0.20	19
Sweating	41	0.19	17
Bradycardia	37	0.17	16
Collapse	37	0.17	24
Dysphagia	30	0.14	8
Disturbed Cutaneous Sensitiveness	28	0.13	10
Other Problems	28	0.13	14
Fever/Elevated Body Temperature	21	0.10	15
Hypertension	21	0.10	14
Arrhythmia	18	0.08	12
Hematoma	18	0.08	13
Emesis	14	0.07	11
Allergic Reaction Local (Flush)	14	0.07	4
Allergic Reaction Systemic	13	0.06	6
Dyspnea	13	0.06	8
Insomnia	13	0.06	3
Hemolysis	12	0.06	10
Tachycardia	11	0.05	9
Prolonged Bleeding Time	11	0.05	11
Edema	11	0.05	7
Shunt Occlusion	9	0.04	7
Restlessness	9	0.04	6
Cough	9	0.04	4

2/ The venous access problems that occurred were puncture pain, missed puncture, needle thrombosis, needle dislocation, and other puncture problems.

Table 3. Adverse Event Summary
For All German Patients (continued) (n =136) See attached table from Germany.

Adverse Event	21306 treatments		
	Total No. of Events		Total No. of Patients Reporting the Complication
	n	(%)	
Bleeding	8	0.04	4
Polyuria	8	0.04	7
Hypoglycemia	5	0.02	4
Hyperventilation	2	0.01	2
Other Rhythm Problems	1	0.01	1
Total	1904	8.94	

Myocardial Infarctions

There were no nonfatal myocardial infarctions (MIs) in the U.S. study; nonfatal MIs were not recorded in the German study. One U.S. and five German patients had fatal MIs during the study.

Table 4. Myocardial Infarctions Summary

	U.S. Study	German Study
Nonfatal Myocardial Infarctions	Zero	Not recorded
Fatal Myocardial Infarctions	One	Five

Deaths

A total of six deaths were reported in the 91 U.S. and German patients enrolled in the clinical studies used to support the premarket approval application (PMA). These deaths are listed and described in Table 3. Since the initiation of the use of the H.E.L.P. system in Germany, a total of 27 deaths have been reported among 441 patients treated over the past decade. None of these deaths occurred during treatment and the clinical investigators did not identify the H.E.L.P. therapy as a causal factor. However, it cannot be concluded with certainty, due to the small size of the patients groups and the lack of a control group, whether any of the deaths were treatment related.

Table 5 Patient Deaths

Patient			History		HELP Treatment			Death Information		
Pt. No.	Age	m/f	CHD/OAD	Infarction	Start	Interval	Last	Date of Death*	Cause	Autopsy
German Study										
002007* 2, Pt. 7	70	f	3-vessel CHD; CABG; shunt implant; PTCA		3/12/87	weekly	9/27/91 (145th treatment)	10/2/91 (5)	Ischemia colitis, Pericardial hemorrhage and tamponade	Y
004042* 4, Pt. 42	50	m	CHD	Infarction	12/23/87	weekly	11/21/88 (49th treatment)	11/21/88 (0)	Acute cardiac death (failure of heart and circulation)	N
005025** 5, Pt. 25	40	m	3-vessel CHD	Recurrent anterior and posterior wall infarction	1/26/88	weekly	4/17/89 (53rd treatment)	5/1/89 (14)	Acute left ventricular insufficiency with cardiogenic shock; reinfarction suspected.	N
007033** 7, Pt. 33	33	f	3-vessel CHD; CABG 3x	Posterior wall infarction	1/16/87	weekly	4/30/87 (14th treatment)	5/3/87 (3)	Recurrent cardiac infarction due to thrombosis known ventricular arrhythmia, severe CHD	Y
008038* 1, Pt. 38	47	m	3-vessel CHD; CABG; aneurysm; surgery	Infarction	5/12/87	biweekly	2/5/91 (109th treatment)	2/16/91 (11)	Myocardial infarction/cardiogenic shock; coronary thrombotic occlusion of the main artery	Y
U.S. Study										
445-460*	47	m	CHD; angina; CABG	Infarction	2/18/91	weekly (q 6m) biweekly (>6 mos)	7/5/93 (72nd treatment)	7/13/93 (8)	Acute anterior wall myocardial infarction	N

*Days after the last HELP treatment in parentheses
Abbreviations: CHD: Coronary Heart Disease; CABG coronary arterial bypass grafting: Aortocoronary Venous Bypass; PTCA: Percutaneous Transluminal Coronary Angioplasty

* Patients in Group C.
** Patients in Group B.

Other Potential Adverse Events

Although patients participating in the clinical study did not experience the following adverse events during the reported 24,132 treatments, such events may occur in procedures involving extracorporeal circulation: uncontrolled bleeding; infectious disease transmission, including hepatitis; sepsis due to circuit contamination; and air embolism.

Other complications may include: plasma loss from circuit leaks; coagulopathy potentially extending several days post treatment; and volume shifts. Equipment malfunction or user error may result in fluid volume abnormalities which may require acute medical intervention.

Reduction in Other Serum Components

LDL-apheresis is known to decrease the selected serum components listed below. The long-term effects of such reduction have not been established.

Plasma Component	#Pts	#Treatments	% Change After Treatment Mean and Range
HDL-C	91	6304	-13.6 (-89.2 to 382.4)
Fibrinogen	91	5519	-58.0 (-98.2 to 306.0)
Apolipoprotein A-1	40	1972	-16.8 (-61.0 to 68.8)
Apolipoprotein B	40	1968	-55.4 (-84.1 to -3.9)
Platelets	5	21	-10.1 (-46.0 to 55.3)
Ferritin*	5	19	-16.0 (-98.0 to 52.9)

* The acute reduction with treatment reported here was associated with an over time reduction in pretreatment ferritin levels from a baseline mean of 69.7 mg/dl to a mean at six months of 23.3 mg/dl in U.S. study patients.

Heparin administration is known to produce, transiently, lipoproteins which may fall into the HDL category but are not true high density lipoproteins in the usual sense. These proteins are removed gradually after heparin in the plasma is metabolized, and the patient's HDL returns to normal. This effect occurs *in vivo* and even in the test tube after the blood is drawn. The phenomenon has been known for decades and is considered harmless to the patient.[1-6]

The distribution of HDL values post H.E.L.P. therapy indicates that the majority of patients have little or no change in their HDL cholesterol on H.E.L.P.

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therapy. However, many patients who have hypertriglyceridemia at the beginning of therapy have an increase in lipoproteins which are measured as HDL, as explained in the preceding paragraph.[4]

Review of the distribution of percentage change indicates that several outliers may have occurred for this measure. If the values indicating a percentage increase in fibrinogen above 40% are considered outliers, the mean percentage increase from -58.0% to -58.5%. Thus, the mean is not seriously affected by the presence of these outliers. Also, the outliers occurred in the area of an increase in fibrinogen; outliers in the opposite direction would be of greater concern clinically as they might indicate potential for a bleeding event.

Routine cellular and chemical studies indicated no clinically significant changes, with the exception of plasma iron and ferritin. Decreases in plasma iron and ferritin levels with an increase in iron-binding capacity indicated the development of mild iron deficiency. Although no evidence of significant anemia developed, patients' ferritin and iron levels should be monitored while on H.E.L.P. therapy and corrective measures taken as appropriate.

Acute changes in CBC are provided in the following table. These changes were measured during the first four treatments for the first five patients in the U.S. study and during the first five treatments for the 51 patients in the German study.

Mean Acute Percent Changes in CBC

Component	Number of Patients	Number of Treatments	Mean Percent Change	Ranges of Percent Change
Hematocrit	56	336	-3.3	-20.4 to 117.1%
Hemoglobin	56	337	-3.8	-54.7 to 15.7%
WBC Count	56	336	17.7	-50.8 to 98.3%
Granulocytes	42	199	5.1	-48.0 to 52.6%
Lymphocytes	55	287	-3.0	-61.1 to 123.8%
Other*	55	279	6.6	-100.0 to 400.00
Platelet Count	56	332	-10.1	-46.0 to 55.3%

*"Other" refers to types of white blood cells other than granulocytes or lymphocytes, including eosinophils, basophils, and reticulocytes.

The hematocrit distribution indicates a single outlying value, a percentage change of 117%. If this value is removed from the calculations, the percent reduction increases from -3.3% to -3.7%. This is not considered a significant

change in the mean and either number gives an overall impression of the direction and extent of the change in hematocrit with a single treatment. The range of values prior to treatment (Table 33 in the original PMA) is 16.4 - 55.0%, and the range of values post treatment is 21.7 - 52.1%. The outlier value occurred in a treatment where the pretreatment reading reported was 16.4% and the posttreatment reading was 35.6%.

The distribution of data regarding WBC indicates no obvious outlying values, but rather a continuum of percent changes. The range of the percentage change may reflect the relatively low value of the actual values, which normally range 4.3 - 10.8 k/cmm. The ranges of the actual values doe not indicate values significantly outside of the normal range: pretreatment values ranged from 3.4 - 15.1 k/cmm and the posttreatment values ranged from 2.8 to 16.7k/cmm.

The percentage changes in granulocytes, lymphocytes, and other indicate no obvious outlying values and no actual values notably outside of the normal ranges for these values. The large percentage changes appear due to a pretreatment value at one end of the normal range and a posttreatment value at the other end of the normal range. Pretreatment and posttreatment ranges are provided below from Table 33 of the original PMA:

	Pretreatment	Posttreatment
Granulocytes (%)	38-84	30-85
Lymphocytes (%)	7-58	10-62
Other	0-16	0-12

These ranges do not indicate the occurrence of findings of significant clinical concern.

Acute changes in Blood Chemistry are provided in the following table. These changes were measured during the first four treatments for the first five patients in the U.S. study and during five treatments for the 51 patients in the German study.

Mean Acute Percent Changes in Blood Chemistry

Parameter	Number of Patients	Number of Treatments	Mean Percent Change	Ranges of Percent Change
Total Protein	5	19	-18.8	-29.6 to -8.1
Albumin	5	19	-15.5	-26.2 to -6.5
Sodium	6	20	0.7	-1.5 to 2.9
Potassium	6	20	0.9	-9.5 to 13.9
Carbon Dioxide	6	20	7.8	-11.5 to 25.0
Chloride	6	20	3.5	0.9 to 6.9
Calcium	5	19	-6.3	-13.1 to -2.2
Phosphorus	5	19	2.0	-17.9 to 22.2
Bilirubin	5	19	19.1	-20.0 to 100.0
Alk. Phosphatase	5	19	-12.4	-21.0 to -6.0
LDH	47	207	-7.2	-66.5 to 81.5
SGOT	5	19	-11.6	-23.3 to 16.7
GGPT	5	19	-25.5	-50.0 to -8.3
CPK	5	19	-43.2	-56.5 to -33.0
Glucose	5	19	-5.6	-55.8 to 25.0
BUN	5	20	-11.5	-23.1 to 0
Creatinine	5	20	-12.3	-22.2 to 0
Uric Acid	5	19	-18.8	-28.3 to -6.9

These data indicate varying degrees of acute changes in these parameters with treatment, although none of these changes are considered clinically significant. The values for normal bilirubin are quite small (generally ranging from 0.3 to 1.0 mg/dl). Percentage changes for these values can appear large with relatively small absolute changes. The range of actual values pretreatment was 0.2 to 0.8, as was the range of values posttreatment. Thus, there do not appear to be any outliers for this variable. Therefore, the mean should adequately represent the effect of H.E.L.P. treatment on bilirubin.

6.1. Notes for Potential Adverse Events

If a patient experiences an adverse event during a procedure, the physician should stop the procedure until the cause of the reaction has been determined and the patient's condition has stabilized. The physician should determine all medical responses to adverse events based upon the individual patient's physical condition. However, certain reactions that may be anticipated are identified below with common medical treatment responses.

(1) Hypotension. The patient should receive increased intravenous fluids and, if necessary, be placed in the Trendelenburg position. If the patient does not respond to intravenous fluids, then the procedure should be terminated.

Note: For an "anaphylactoid" like reaction, administration of epinephrine, sympathomimetic drugs, prednisolone, anti-histamines, and/or calcium have been reported by clinicians as effective interventions.

(2) Nausea and Vomiting. The etiology of the nausea or vomiting should be investigated, and if associated with hypotension, as is often the case, the patient should receive intravenous fluids and, if necessary, should be placed in the Trendelenburg position. If the nausea or vomiting persists despite increased intravenous fluids, then the procedure should be terminated.

(3) Flushing/Blotching. Check vital signs and reduce the blood flow rate. If symptoms are persistent or repetitive, consider the administration of Benadryl.

(4) Angina/Chest Pain. Appropriate medical therapy should be instituted at the discretion of the physician. If the angina persists despite adequate medical therapy, then the procedure should be terminated.

(5) Fainting/Lightheadedness. See hypotension.

(6) Anemia. May be minimized by the appropriate use of iron supplements. Clinical symptoms may appear when hemoglobin is below 11 g/dl in men and 10 g/dl in women.

(7) Prolonged Bleeding (at cannulation site after removing venous cannulae). Direct manual pressure should be applied until the bleeding stops. If prolonged bleeding occurs (in excess of 20 minutes), adjustment of the heparin dosing may be necessary. It is recommended that during the subsequent procedure, the heparin dose be reduced and monitored by Activated Clotting Time (ACT). Repetitive LDL-apheresis treatment may affect the patient's clotting time. Therefore, a periodic check, e.g., every three months, of other relevant coagulation parameters is recommended, including number of platelets and fibrinogen concentration, in order to ensure that these parameters are sufficient to maintain adequate coagulation.

(8) Hemolysis as Evident by Discoloration of Plasma or Hemolysis as Indicated by Activation of the Blood Leak Detector of the Plasmat-secura Machine. If either indicator of hemolysis occurs, the procedure should be terminated and the patient's hematocrit, urine output and kidney function monitored.

7.0 Clinical Experience

Two clinical studies, one in Germany and one in the U.S., were conducted to evaluate the safety and efficacy of the H.E.L.P. System in the treatment of hypercholesterolemia that was not adequately controlled by diet and drug therapy.

A total of 91 patients were studied at 13 centers in the U.S. and Europe; 77 of these were treated for at least six months with weekly treatments. Of these 91 patients, 66 met the definitions for target patient populations. A total of 6,419 treatments were given in the two studies. The studies did not include the following subjects: patients less than 15 years of age; women of child-bearing potential; patients with hypothyroidism, congestive heart failure, major arrhythmia, renal insufficiency, uncontrolled diabetes mellitus, malignancy, dementia, disorders associated with excessive bleeding, intracranial disease which might cause bleeding if the patient was anticoagulated, triglycerides > 500 mg/dl, or diastolic blood pressure > 100 mmHg; patients positive for acute Hepatitis (type A or B) or HIV (or diagnosis of AIDS); patients treated with anticoagulants; or immunosuppressed patients.

Patients were treated weekly for six months and biweekly for six months in the U.S. study. In the German study patients were treated weekly for two years. In both studies, patients were offered continued H.E.L.P. therapy thereafter. During the study period, patients were maintained on diet and maximum tolerated lipid-lowering therapy.

Effectiveness results were reported for mean pre-treatment to post-treatment changes (acute effect). For 6,193 weekly H.E.L.P. treatments with LDL-C data, a mean acute reduction in LDL-C of 59.9% was obtained from pre- to post-treatment. However, the LDL-C levels rebounded at a non-linear rate (the rise was steeper during the first four days following therapy) as shown in the figure and table below. Calculation of chronic reductions showed mean LDL-C levels were reduced by 45.7% for the interval.[7]

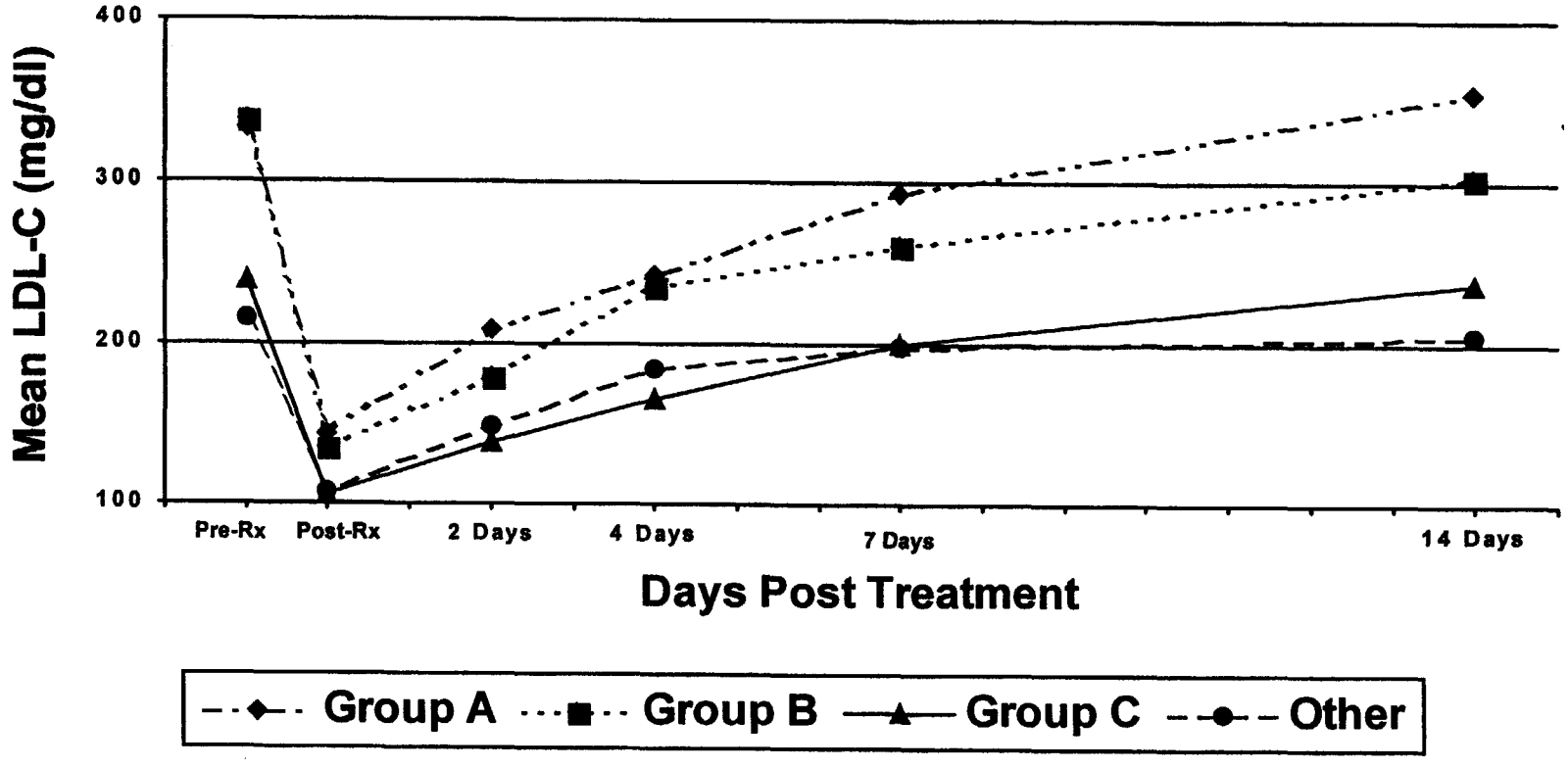
Mean LDL-C (mg/dl)
400
300
200
100
Pre-Rx
Post-Rx
2 Days
4 Days
7 Days
14 Days
Days Post Treatment
Group A
Group B
Group C
Other

Table 6. Range of rebound of LDL-C after treatment during study period

Number of Days After Treatment	Cumulative Mean Percentage Rebound to Baseline			
	Group A (1 patient, 3 treatments)	Group B (1 patient, 2 treatments)	Group C (2 patients, 3 treatments)	Other * (9 patients, 13 treatments)
2	62 - 64	51 - 55	46 - 64	50 - 104
4	68 - 80	60 - 81	56 - 80	74 - 136
7	81 - 100	71 - 86	68 - 95	81 - 140
14	94 - 123	73 - 110	94 - 102	84 - 116

* One patient studied in the kinetics substudy had an LDL-C level of 124 mg/dl prior to treatment. That patient's levels rose to 174 mg/dl during the follow-up period which represents 140% of the baseline level. When that patient is removed from the analysis the upper value of the ranges decreases substantially at each day: 24% on day 2, 93% on day 4, and 104% on day 7.

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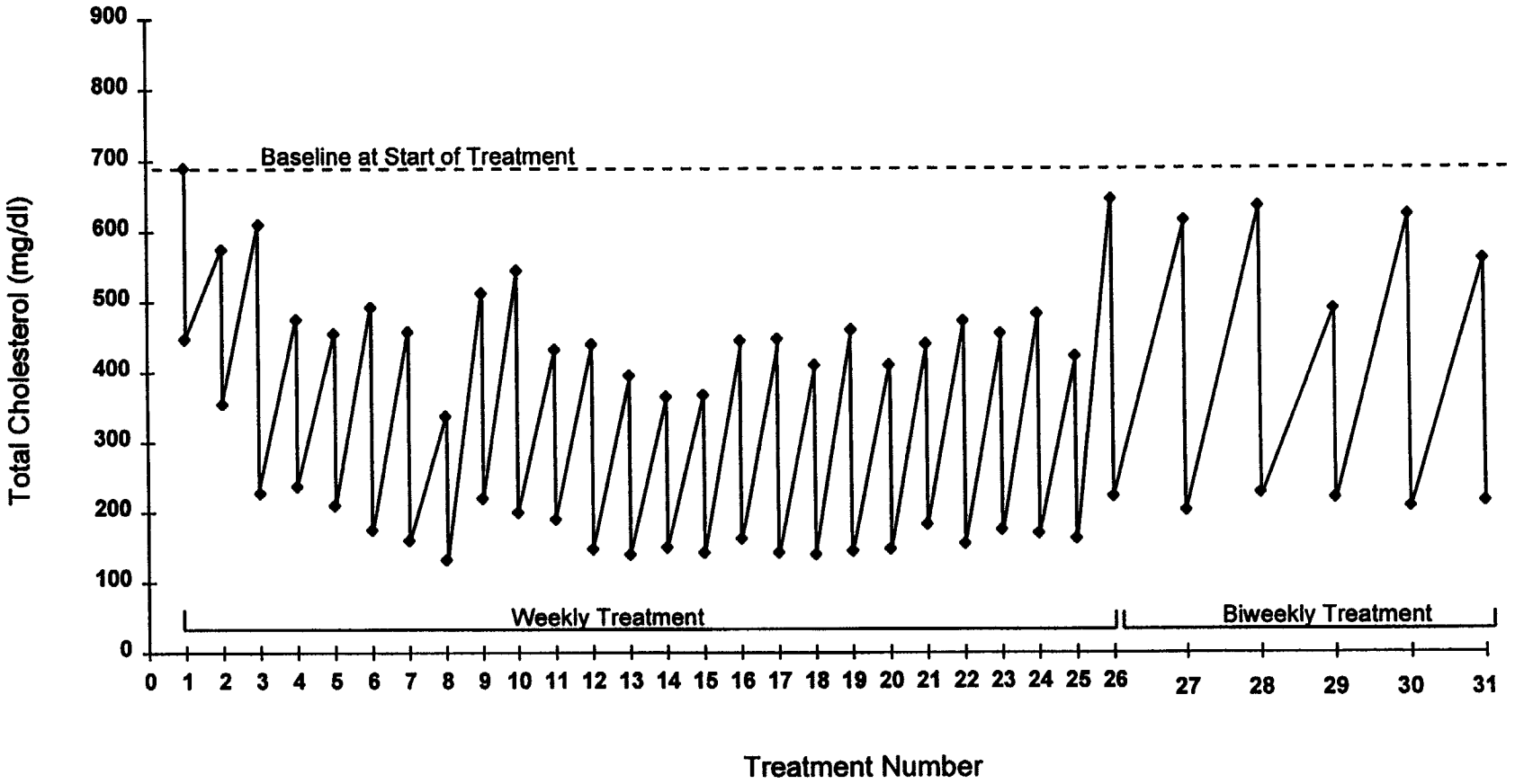
Total Cholesterol Levels in a Homozygote Patient Receiving H.E.L.P. Therapy



Without regular treatments, a patient's LDL-C and total cholesterol levels will rebound to pretreatment levels achieved with diet and drug therapy. With weekly H.E.L.P. treatments, a patient's cholesterol levels can be maintained well below the pretreatment levels. As shown in the chart titled "Total Cholesterol Levels in a Homozygote Patient Receiving H.E.L.P. Therapy," total cholesterol levels were maintained at a lower level when the patient received weekly treatments than when biweekly treatments were given.

Coronary angiography was carried out to assess changes in the degree of stenosis of coronary artery lesions. Results were published by Schuff-Werner et al. in the *European Journal of Clinical Investigations* in 1994.[8]

Adverse events data were reported from the U.S. clinical study (40 patients and 2,826 treatments) through October 1995 and from all German patients treated at the H.E.L.P. centers that participated in the clinical study (21,306 treatments in 136 patients) through 1995. The adverse events experienced by these patients during the H.E.L.P. System treatment program are summarized above in Tables 1 and 2 in Section 6.0. All deaths and myocardial infarctions experienced by patients who were treated with the H.E.L.P. System during that time period are also reported in Section 6.0.

8.0 Instructions for Use

The H.E.L.P. System is indicated for use in performing low density lipoprotein cholesterol (LDL-C) apheresis to acutely remove LDL-C from the plasma of the following high risk patient populations for whom diet has been ineffective and maximum drug therapy has either been ineffective or not tolerated:

Group A	Functional Hypercholesterolemic Homozygotes with LDL-C > 500 mg/dl
Group B	Functional Hypercholesterolemic Heterozygotes with LDL-C ≥ 300 mg/dl; and
Group C	Functional Hypercholesterolemic Heterozygotes with LDL-C ≥ 200 mg/dl and documented coronary heart disease.

The LDL-C levels for the indicated patient populations are baseline LDL-C levels obtained after the patient has had, at a minimum, a six-month trial of an American Heart Association (AHA) Step II diet (or equivalent) and maximum tolerated combination drug therapy designed to reduce LDL-C. Maximum tolerated combination drug therapy is an adequate trial of drugs from at least two separate classes of hypolipidemic agents such as bile acid sequesterants, HMG-CoA reductase inhibitors, fibric acid derivatives, niacin/nicotinic acid, etc. Documented coronary heart disease (CHD) includes documentation of coronary heart disease by coronary angiography or a history of myocardial infarction (MI), coronary artery

bypass surgery (CABG), percutaneous transluminal coronary angioplasty (PTCA) or alternative revascularization procedure (e.g., atherectomy or stent), or progressive angina documented by exercise or non-exercise stress test.

Effectiveness of the therapy will be influenced by the treatment frequency and amount of plasma treated.

Determining treatment frequency:

Prior to initiation of therapy, baseline lipid levels should be determined after stabilization on maximum diet and drug therapy by taking two measurements during a two to four week period. (Note: The two values should be within 10% of each other to be acceptable.)

Treatment with LDL-apheresis provides an immediate acute reduction in a patient's lipid levels compared to pre-treatment lipid levels. The acute effects of an LDL-apheresis treatment on LDL-C, total cholesterol, and HDL-C with each H.E.L.P. treatment for each of the three population subgroups are shown below.

Table 7. Acute Percent Change (Mean and Range) Across Each Treatment*

Patient Subgroup	LDL-C	Total Cholesterol	HDL-C
Group A (4 patients)	-63.6 (-78.1 to -24.5) n =395	-57.3 (-70.1 to -24.5) n = 395	-17.1 (-46.1 to 24.0) n = 395
Group B (32 patients)	-62.0 (-95.2 to -5.0) n = 2349	-51.9 (-76.2 to -4.1) n = 2362	-12.8 (-75.9 to 231.0) n = 2351
Group C (30 patients)	-59.8 (-91.4 to -8.8) N = 2266	-48.9 (-77.7 to -2.0) n= 2331	-13.7 (-89.2 to 382.4) n = 2318

*n = number of treatments

Heparin administration is known to produce, transiently, lipoproteins which may fall into the HDL category but are not true high density lipoproteins in the usual sense. These proteins are removed gradually after heparin in the plasma is metabolized, and the patient's HDL returns to normal. This effect occurs *in vivo* and even in the test tube after the blood is drawn. The phenomenon has been known for decades and is considered harmless to the patient.[1-6]

The distribution of HDL values post H.E.L.P. therapy indicates that the majority of patients have little or no change in their HDL cholesterol on H.E.L.P. therapy. However, many patients who have hypertriglyceridemia at the beginning

of therapy have an increase in lipoproteins which are measured as HDL, as explained in the preceding paragraph.[4]

Therapy with the H.E.L.P. System does not produce a sustained lowering of lipid levels. A patient's LDL-C level will increase (or rebound) immediately after treatment at a non-linear rate (more rapidly immediately post-treatment) as shown in the following table:

Time Interval	Group A (1 patient, 3 treatments) mg/dl	Group B (1 patient, 2 treatments) mg/dl	Group C (2 patients, 3 treatments) mg/dl	Other (9 patients, 13 treatments) mg/dl
Day 0, Pretreatment	332.7 (274-372)	338.0 (304-372)	238.7 (227-250)	214.8 (124-287)
Day 0, Posttreatment	143.3 (139-146)	134.5 (134-135)	106.0 (77-128)	107.7 (69-151)
Day 2	208.3 (175-231)	179.5 (168-191)	138.3 (115-154)	148.3 (99-201)
Day 4	242.7 (219-255)	235.5 (225-246)	164.3 (141-190)	183.5 (129-235)
Day 7	294.3 (274-306)	261.5 (260-263)	199.0 (171-226)	197.3 (144-246)
Day 14, Pretreatment	354.7 (337-375)	304.0 (273-335)	236.7 (229-246)	205.2 (109-267)
Day 14, Posttreatment	140.0 (135-145)	121.5 (108-135)	110.0 (85-125)	111.0 (65-166)

With regular apheresis treatments, a patient's LDL-C level can be maintained below the baseline level. Without regular treatment, a patient's LDL-C level will rebound to the baseline or higher. In addition, the rate of rebound shown will accelerate if diet and lipid-lowering drug therapy are discontinued. Therefore, a patient's diet and drug therapy must be continued.

Because of the heterogeneous nature of hypercholesterolemia, dosing and response therapy vary among patients, resulting in the need for individualized treatment prescriptions. It is recommended that, shortly after the initiation of therapy, the physician measure a rebound curve for each patient to aid in determining the appropriate treatment interval. Rebound curves are determined by measuring the patient's lipid level immediately following the treatment and at several intermediate points before the next treatment. If the patient changes or discontinues lipid-lowering medication while undergoing LDL-apheresis, the rebound curve should be reestablished.

Data from the clinical studies using the H.E.L.P. System have suggested that patients in Groups A and B of the indicated population should be treated at a frequency of once a week, while patients in Group C should be treated once every two weeks as part of a life-long maintenance therapy.

Plasma Volume to Be Treated

The effectiveness of H.E.L.P. System treatment in lowering LDL-C levels was established in clinical studies by treating about one plasma volume. For the average adult, one plasma volume equals approximately 3 liters (about 3 quarts) of plasma.

Determining Heparin Dosage

In adult patients weighing between 50 and 90 kg, the sensitivity to heparin does not appear to be related to body weight. Within this population there is no reason to modify the suggested heparin doses by body weight.

Before H.E.L.P. treatment begins, an activating clotting time (ACT) is drawn as a baseline. If the ACT is within the normal range of 120 to 196 seconds, H.E.L.P. patients receive 3,000 units of heparin (porcine) intravenously immediately before starting H.E.L.P. treatment. Before H.E.L.P. treatment begins, the heparin pump is set to deliver 3cc per hour of a 50/50 solution of heparin and saline, (5,000 units of heparin/5cc saline), or 1,500 units of heparin an hour. Shortly after treatment has started, 2,000 units of heparin are injected into the arterial line through the port proximal to the blood pump. Halfway through treatment, an ACT is drawn from the same port. If the ACT is in the mid to high normal range or above, the heparin pump is reduced to 1.5cc per hour. If results of the ACT are in the lower range of normal, the heparin pump is maintained at 3cc per hour until the last 500cc of treatment, and then reduced to 1.0cc per hour.

After treatment is finished, an ACT is drawn directly from the patient's arterial access line before the needle is removed. If the ACT is below 200, the arterial and venous needles are removed. If the Act is above 200, the arterial needle stays in, and the ACT is repeated every 15 to 20 minutes until the ACT is below 200.

If for any reason there is evidence during treatment that the ACT is low, *i.e.*, the plasma filter is clotting as evidenced by an elevated AP2 that is not reduced by the addition of a saline drip, the ACT is tested. If the ACT is in the low normal range, an additional 1,000 to 2,000 units of heparin may be added.

H.E.L.P. System Solutions

The following five solutions are used extracorporeally in the H.E.L.P. System treatment: (1) 0.9% sodium chloride solution; (2) heparin sodium solution 10,000 I.U./ml; (3) sodium acetate buffer solution; (4) acidic bicarbonate hemodialysis concentrate HDY 320; and (5) 5% bicarbonate concentrate. Sodium chloride is used for rinsing and priming the assembled lines and filters prior to treatment and is hung from the IV pole. The sodium acetate buffer solution (pH4.85) is used to adjust the plasma to the optimal pH (5.12) for the LDL cholesterol with heparin and is hung from the IV pole. Heparin sodium solution is injected into the buffered solution and mixed with plasma to precipitate the cholesterol and is contained in a glass bottle. The acetic bicarbonate hemodialysis concentrate and alkaline bicarbonate hemodialysis concentrate are used for bicarbonate hemodialysis to remove acetate from the treated plasma and to restore the plasma to physiological pH for reinfusion to the patient and is contained in plastic containers. A more detailed description of how the H.E.L.P. System solutions are connected to the H.E.L.P. System disposables is available in the Operator's Manual. Color coding of the disposable components ensures that they are connected properly to each other and to the device. The physicians, nurses, and technicians will learn how to connect the bags and containers with the solutions during their H.E.L.P. System training.

The solutions will be provided by Braun. The 0.9% sodium chloride solution, the heparin sodium solution, and the sodium acetate buffer solution will be provided sterile by the pharmacy; the acidic bicarbonate hemodialysis concentrate HDY 320 and the 5% bicarbonate concentrate will not be provided sterile and they will not require sterilization by the user.

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A PATIENT GUIDE TO THE H.E.L.P. SYSTEM

I. What is low-density lipoprotein (LDL) cholesterol and why are you considered a candidate for LDL-apheresis?

Cholesterol is a waxy substance that is important for membranes and hormone production in the body. It is carried on particles in the blood stream known as lipoproteins which contain cholesterol as well as protein. The major cholesterol-carrying lipoprotein or particle in the blood stream is known as low-density lipoprotein or LDL. High levels of LDL cholesterol have been associated with an increased risk of heart disease, and LDL causes clogging of arteries by being deposited directly into the artery wall. Lowering LDL cholesterol levels in the bloodstream with diet and/or drug therapy has been shown to reduce the risk of coronary heart disease. 1/ An LDL cholesterol level of greater than or equal to 160 mg/dl has been classified by the National Cholesterol Education Program as a high-risk LDL level for heart disease. It is recommend that all patients get their LDL cholesterol levels to below 160 mg/dl, and that patients with established heart disease have their LDL cholesterol lowered to less than 100 mg/dl, if possible.

You are being considered as a candidate to receive LDL-apheresis therapy because, even though you receive cholesterol-lowering diet and drugs, your LDL-cholesterol level is above a level regarded as being healthy for you.

There are three groups of patients who are candidates for the procedure known as LDL-apheresis because they have not responded adequately to maximum diet and drug therapy for at least six months:

Group A. Patients with functional homozygous hypercholesterolemia, defined as an LDL-cholesterol level above 500 mg/dl.

Group B. Patients with an LDL-cholesterol level above 300 mg/dl. Most patients in this group are severe functional hypercholesterolemic heterozygotes.

Group C. Functional hypercholesterolemic heterozygotes with an LDL-cholesterol level above 200 mg/dl with documented coronary heart disease (CHD).

If you meet any of the above criteria for treatment with the H.E.L.P. (Heparin-Induced Lipoprotein System) System, and, after reading this guide and discussing it with your physician, you choose this therapy, you must also agree to

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1/ Scandinavian Simvastatin Survival Study Group, "Randomized trial of cholesterol lowering in 4,444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S)." Lancet 1994; 344:1383-1389.

participate in a Patient Registry in order to receive treatment. Participation will require reporting of certain information on your treatment and laboratory data assessments for as long as you receive treatment.

With regular apheresis treatments, your LDL cholesterol level can be maintained below the baseline LDL cholesterol level. Without regular treatment, your LDL cholesterol level will rebound to the baseline or higher. In addition, the rate of rebound shown will accelerate if diet and lipid-lowering drug therapy are discontinued. Therefore, your diet and drug therapy must be continued.

II. Alternatives

Diet and cholesterol-lowering drug therapy will adequately control LDL-cholesterol levels in most patients. Some patients with severe hypercholesterolemia need further therapy for lowering LDL-cholesterol. Surgical procedures such as portacaval shunt, partial ileal bypass surgery and liver transplantation are alternatives that lower LDL-cholesterol. These surgical treatments may have significant complications and do not always achieve adequate LDL-cholesterol reduction.

Plasma exchange, a procedure similar to LDL-apheresis, is also an alternative therapy. This treatment, like H.E.L.P. therapy, is non-specific and removes the beneficial parts of plasma, such as HDL, as well as the LDL.

You should review these alternatives with your physician.

III. How this guide can help you.

This Patient Guide provides basic information in response to general questions that you are likely to have. However, you should review any questions that you may have with your individual physician, who is familiar with your specific medical condition. Treatment with this medical device must be prescribed by a physician and conducted by a doctor trained in its specific use.

IV. What is LDL-apheresis?

LDL-apheresis is a type of "extracorporeal" (blood taken outside the body) procedure to remove LDL-cholesterol from the blood.

V. How is LDL-apheresis performed?

LDL-apheresis circulates a portion of the blood outside the body, separating the plasma (the liquid in which the cells are suspended) from the whole blood, removing the LDL-cholesterol and then returning the plasma and blood back to the patient. The procedure is used for patients in whom diet and maximum lipid-

lowering drug therapy have not adequately controlled very high LDL-cholesterol levels. The LDL-apheresis method proposed for your therapy uses the H.E.L.P. System.

VI. What is the H.E.L.P. System?

The H.E.L.P. System consists of three parts that are used and then discarded after each treatment and an automated machine that controls and checks the LDL-apheresis procedure. The disposable parts include a series of four filters, five solutions, and a tubing set designed specifically for the H.E.L.P. System. One of the five solutions is a heparin buffer solution that reacts with the plasma to precipitate the LDL-cholesterol. This precipitate is then filtered out of the plasma.

Photograph of System to be Inserted

The H.E.L.P. System has been in use in Europe for over ten years. In the U.S., the H.E.L.P. System has been tested in four centers in 40 patients, 19 of whom were within the indicated population for the device. The majority of the patients in the U.S. study had high LDL-cholesterol levels that were not lowered by diet and maximum lipid-lowering drug therapy consistent with an inherited disorder in cholesterol metabolism. Some of these patients already had coronary artery disease. The study showed that the H.E.L.P. System is effective in acutely lowering LDL-cholesterol after single and repeated treatments but, as explained later, your LDL-cholesterol level will increase (or rebound) again after each treatment.

VII. How does the H.E.L.P. System work?

In simplest terms, LDL-apheresis using the H.E.L.P. System requires: (1) withdrawal of blood from a vein through a needle, most commonly from your arm, and return of your blood to your other arm after removal of the LDL-cholesterol; (2) a blood thinner called heparin to prevent your blood from clotting outside of your body; and (3) the disposable system filters, solutions, and tubing. Each part of the LDL-apheresis treatment is described in more detail below.

1. Access to blood. The primary goal in blood access is to obtain adequate blood flow for the procedure as safely as possible. Arm veins are usually sufficient for the LDL-apheresis because low blood flow rates are required (50-100 ml/min). In clinical studies, blood access difficulties occurred in fewer than 2 percent of LDL-apheresis treatments, and most often these were dislocation of the needle from the vein, poor blood flow, or pain at the needle site. Poor vascular

access could require placement of a shunt or catheter in the subclavian vein, but this is uncommon.

2. Anticoagulation (blood thinning). Anticoagulation is required for all procedures where blood is removed from the body. Heparin is used in this procedure. Typically, the patient receives a heparin bolus (a rapid injection) of 3000 USP units of heparin per hour. The blood thinning effects of the heparin may be observed several hours after completing the procedure, and the patient must be careful during that time period to prevent trauma or other injury which might result in excessive bruising or bleeding.

3. LDL-apheresis system (See figure below). After access to the blood is obtained and the blood is thinned, the blood enters the LDL-apheresis system, which includes filters, solutions, tubing, and a monitor/control machine (Plasmat-secura). All parts of the system that come in contact with the patient's blood and plasma are sterile, are used for one treatment only, and are discarded after use.

Insert Schematic of H.E.L.P. System

i. The first step is the separation of the plasma from the whole blood using a membrane plasma separator.

ii. The plasma meets the heparin buffer solution at which time a reaction occurs, allowing the LDL-cholesterol to be filtered. The LDL-reduced plasma then flows through a series of three other filters removing excess heparin and fluids. The plasma is combined with the blood and returned to the patient.

iii. The Plasmat-secura is an automated machine that checks and controls the procedure from start to finish. The H.E.L.P. System has several built-in safety features, including air detectors and various alarms. The procedure takes approximately 1.5 hours to perform.

VIII. How does LDL-apheresis affect your elevated LDL-cholesterol level?

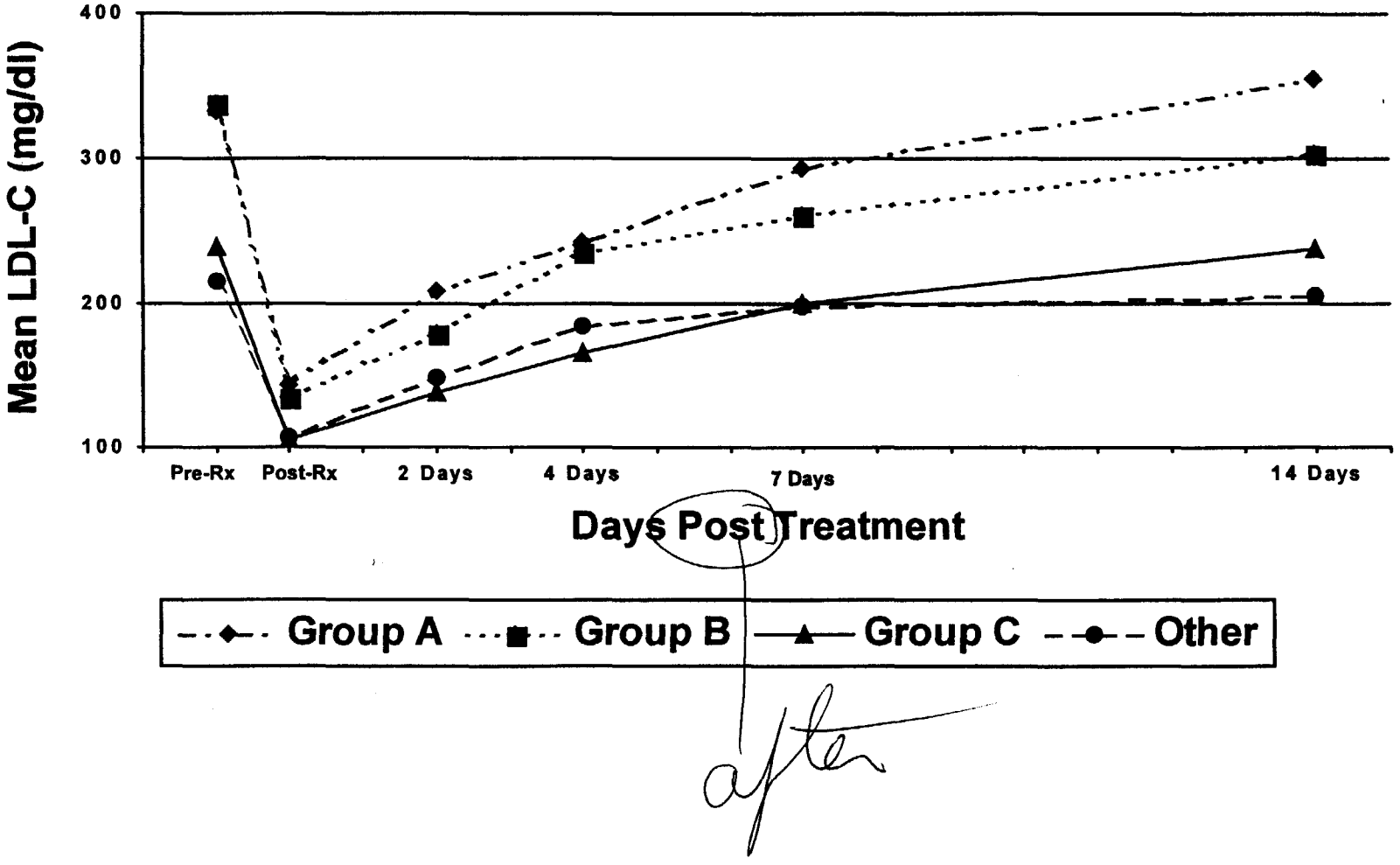
LDL-apheresis can lower your LDL-cholesterol level approximately 60 percent after a single procedure. This lowering is determined by the amount of your plasma passed through the circulatory system during the procedure.

In most cases, to achieve an approximately 60 percent lowering of your LDL-cholesterol level, your physician will treat about one plasma volume. For the

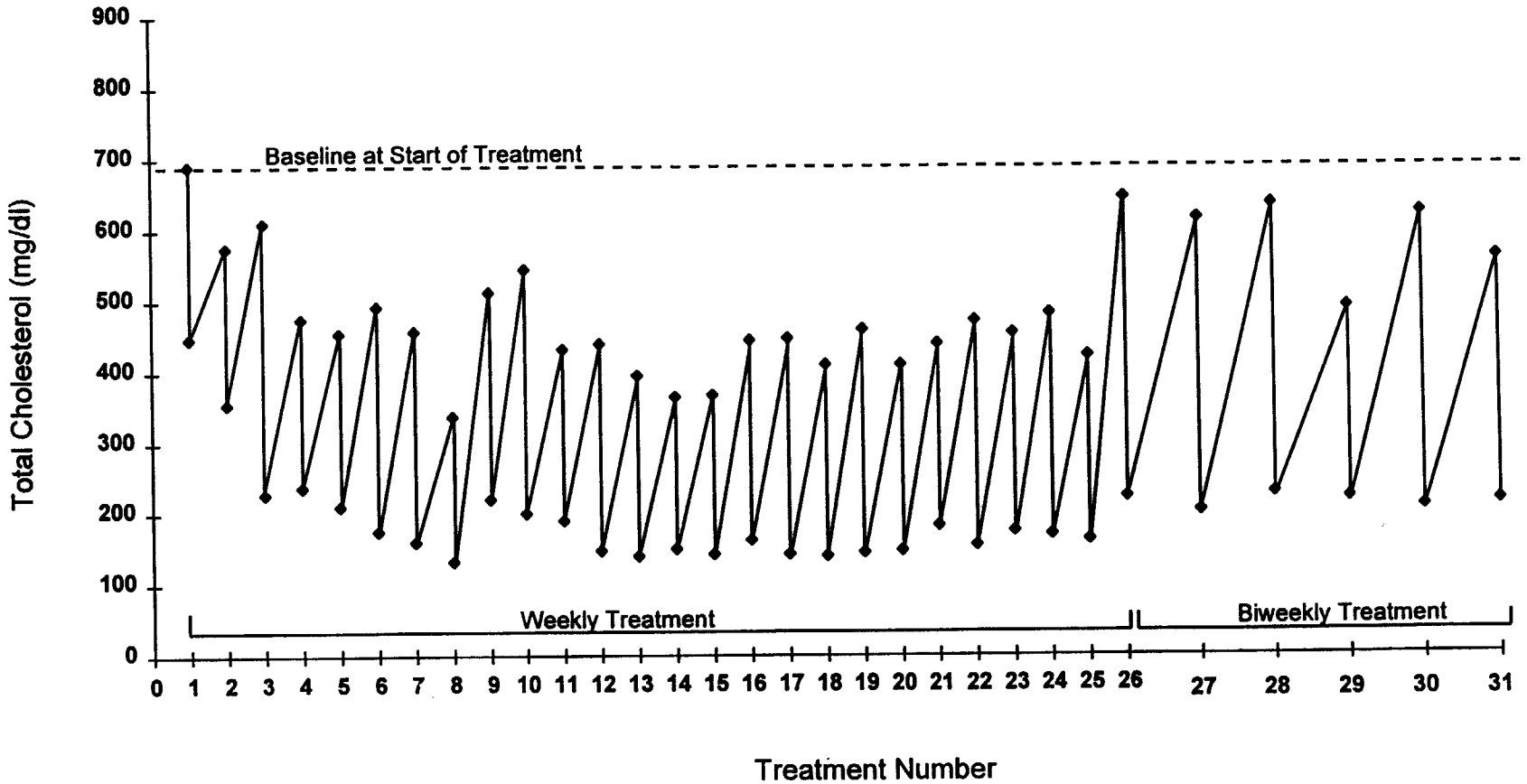
average adult, one plasma volume equals approximately 3 liters (about 3 quarts) of plasma.

1 plasma volume in an average adult = 3 liters (about 3 quarts)
1 plasma volume treated = approximately 60% lowering of LDL-cholesterol

The approximately 60 percent lowering of your LDL-cholesterol level during a single LDL-apheresis treatment is not maintained after the procedure. Because your elevated LDL-cholesterol level is the result of a metabolic defect and LDL-apheresis does not correct the underlying problem, your LDL-cholesterol level begins to increase (or rebound) immediately after treatment. If another LDL-apheresis treatment is not performed, your LDL-cholesterol level will return to your baseline levels on diet and maximum drug therapy in about two weeks. The figure below shows the increase in LDL-C following treatment with the H.E.L.P. System.


Mean LDL-C (mg/dl)
400
300
200
100
Pre-Rx
Post-Rx
2 Days
4 Days
7 Days
14 Days
Days Post Treatment
Group A
Group B
Group C
Other

Total Cholesterol Levels in a Homozygote Patient Receiving H.E.L.P. Therapy



Without regular treatments, your LDL-C and total cholesterol levels will rebound to pretreatment levels achieved with diet and drug therapy. With weekly H.E.L.P. treatments, your cholesterol levels can be maintained well below the pretreatment levels. As shown in the chart titled "Total Cholesterol Levels in a Homozygote Receiving H.E.L.P. Therapy," total cholesterol levels were maintained at a lower level when the patient received weekly treatments than when biweekly treatments were given.

For LDL-apheresis treatment to maintain a lower level of LDL-cholesterol in your blood, you must repeat the procedure regularly. The frequency of your LDL-apheresis treatment is determined by your starting LDL-cholesterol level and the degree of lowering that is achieved during a single procedure.

Please note that LDL-apheresis is a life-long therapy that must be performed at the prescribed frequency. Although the clinical benefits of lowering the LDL-cholesterol have been well supported, the long term clinical benefits of the LDL-cholesterol lowering from use of the H.E.L.P. System, such as the reduction/prevention of coronary heart disease, have not been shown.

In general, individuals with LDL-cholesterol levels starting above 300 mg/dl after diet and maximum drug therapy will be treated once per week, and individuals with LDL-cholesterol levels starting between 200 mg/dl and 300 mg/dl will usually be treated once every two weeks. **It is important to continue your diet and cholesterol-lowering medications after starting LDL-apheresis.** The rate of rebound in your LDL-cholesterol level will increase if you do not continue your lipid-lowering drug therapy.

IX. Safety of LDL-Apheresis.

Note: A detailed explanation of risks and adverse reactions associated with LDL-apheresis should be provided by your physician.

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Selectivity:

Although LDL-apheresis is very selective in removing LDL-cholesterol, there are other parts of your plasma that are partially removed. Most important are HDL-cholesterol, fibrinogen, plasma proteins, and platelets. The following chart shows the average reductions in these plasma parts during the clinical study in the U.S. In most cases, these reductions do not pose a risk to your health. However, your physician will determine the levels of these plasma components before and after treatment periodically to check for any changes of clinical importance.

During the clinical study, decreases in plasma iron and ferritin levels with an increase in iron-binding capacity were observed, indicating the development of mild iron deficiency. Although no evidence of significant anemia developed in the study, your physician will monitor your ferritin and iron levels and take corrective action if appropriate.

Plasma Component	% Change After Treatment Mean and Range for Patients in All Three Group (Mean and Actual Value Range)
HDL-C	-13.6 (-89.2 to 382.4 mg/dl)
Fibrinogen	-58.0 (-98.2 to 306.0 mg/dl)
Apolipoprotein A-1	-16.8 (-61.0 to 68.8 mg/dl)
Apolipoprotein B	-55.4 (-84.1 to -3.9 mg/dl)
Platelets	-10.1 (-46.0 to 55.3 k/cm)
Ferritin*	-16.0 (-98.0 to 52.9 ng/ml)

* The acute reduction with treatment reported here was associated with an over time reduction in pretreatment ferritin levels from a baseline mean of 69.7 ng/dl to a mean at six months of 23.3 ng/dl in U.S. study patients in all three groups.

Adverse Reactions:

Adverse reactions associated with LDL-apheresis are those expected in any procedure involving the circulation of blood outside the body. The problems most frequently reported in the U.S. and German clinical studies included the following: vascular access difficulties; swelling of the face and hands; angina pectoris; hypotension; fatigue; headache; burning eyes; vertigo; nausea; chills and shivering; muscle, bone, and joint pain; puncture pain;

prolonged blood clotting time; vomiting; and gastrointestinal complaints. A total of six deaths were reported in the U.S. and German patients enrolled in the clinical studies. None of these deaths occurred during treatment and the clinical investigators did not identify the H.E.L.P. therapy as a causal factor. However, it cannot be concluded with certainty, due to the small size of the patients groups and the lack of a control group, whether any of the deaths were treatment related.

Other adverse reactions in the clinical studies included the following: sweating; bradycardia; collapse; dysphagia; disturbed cutaneous sensitivity; hypertension; chest heavy/pain; dizziness or fainting; diffuse body ache; elevated temperature; gastrointestinal bleeding; flushing; hyperventilation; wheezing; elevation of liver enzymes; apical density on chest X-ray; ankle swelling; prostatitis; hematuria; hypoglycemia; sympathetic reflex dystrophy; angina/second PTCA; endarterectomy; hematoma; arrhythmia; hemolysis; systemic allergic reaction; dyspnea; insomnia; tachycardia; edema; shunt occlusion; restlessness; cough; bleeding; polyuria; needle thrombosis; and hyperventilation.

Because certain medications, such as diuretics and anti-hypertensive drugs, should not be taken the day before or the day of your treatment, consult with your doctor about all the medications which you are taking.

If you have a hypotensive reaction during treatment, it can usually be corrected by giving you intravenous (IV) fluids. Rarely, it may require temporarily stopping your treatment and placing your head down and raising your legs (Trendelenburg position). In most cases, the hypotension will go away and your treatment can continue.

Because of your elevated LDL-cholesterol level, you may already have heart disease or are at risk for heart disease. Therefore, the possibility of chest pain or heart attack during LDL-apheresis therapy cannot be totally ruled out. During the U.S. and German clinical studies, 31 patients experienced angina. It should be noted in the German study, which was restricted to patients with CHD, the prevalence of angina was reduced from 82% to 35% in two years. There were no non-fatal myocardial infarctions (MIs) during the U.S. clinical study; non-fatal MIs were not recorded in the German study. One U.S. and five German patients had fatal MIs during the studies. Therapy with this device may not rule out the need for a surgical intervention procedure, such as coronary artery bypass graft (CABG), Percutaneous Transluminal Coronary Angioplasty (PTCA), or other revascularization interventions.

Other complications may include: hypocoagulopathy (bleeding tendency) for several days, infectious disease transmission, sepsis (infection) due to circuit contamination, air embolism (entry of air into your bloodstream), hypersensitivity (allergy), and fluid volume shifts (too little or too much fluid in your bloodstream).

Most adverse reactions that occur during the LDL-apheresis procedure will resolve completely upon completion of the treatment. Due to the small size of the study and the lack of a control group, it cannot be concluded whether any of the cardiac events or deaths were treatment related.

X. What you can do to minimize adverse reactions.

1. Do not have the procedure on an empty stomach. Make sure you eat and drink adequately before the procedure. Do not drink alcohol 24 hours before your treatment. If fasting blood samples are necessary, bring some food to eat while you are being treated.

2. Do not perform strenuous exercise on the day of your procedure.

3. Do not take other anti-hypertensive (for high blood pressure) medication, including diuretics, on the day of treatment until after your LDL-apheresis procedure. Again, talk with your physician before stopping your medication.

4. Your physician may prescribe an iron supplement if you develop an iron deficiency anemia.

5. Avoid activities increasing the risk of physical injury for 24 hours after your treatment because of the blood thinning medication used.

GLOSSARY

Air embolism: entry of air into the bloodstream

Anemia: inadequate number of red blood cells

Angina: cardiac related chest pain

Anticoagulation: blood thinning

Anti-hypertensive medications: medications for lowering high blood pressure

Arrhythmia: irregular heartbeat

Bolus: a relatively large volume of fluid given intravenously (IV) and rapidly to magnify a response

Bradycardia: slow pulse

Dysphagia: difficulty in swallowing

Dyspnea: labored breathing

Edema: excess fluid in the intercellular tissue spaces of the body

Extracorporeal: outside the body

Genetic: inherited or acquired

Hypersensitivity: allergy

Hypertension: high blood pressure

Hypocoagulopathy: bleeding tendency

Hypoglycemia: low blood sugar

Hypotension: low blood pressure

Plasma: the liquid in which blood cells are suspended

Polyuria: passage of a large volume of urine in a given period of time

Sepsis: infection

Tachycardia: fast pulse

Trendelenburg position: head placed down and legs raised

Vertigo: dizziness

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